A Thesis Entitled

SOME CHEMISTRY RELATING TO TURMERONES

by

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Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Warwick.

The work described herein was performed at the Department of Chemistry and Molecular Sciences of the University of Warwick, September 1982 to September 1983, and in the Department of Organic Chemistry, School of Chemistry, University of Newcastle upon Tyne, October 1983 to September 1985.

SEPTEMBER, 1985

Acknowledgements

The work described in this thesis was supervised mainly by Professor Bernard T.Golding, and any merits this work may have can be traced to his teaching and direction. As mentor, guide and teacher, he showed me the methods of research, helped me during the difficult times, and tapped the sources of finance when it was necessary. I take this opportunity to thank him for all his efforts on my behalf, which made this work not only possible, but also enjoyable and immensely rewarding. My thanks must go as well to my supervisor at the University of Warwick, Dr Christopher J.Samuel, for the many helpful discussions, and the patience and support he gave me during these years.

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Finally, I would like to thank Elizabeth MacKay for typing the manuscript.

Declaration

The work described in this thesis was performed at the University of Warwick from September 1982 to September 1983, and at the University of Newcastle, 1983-1985. The author declares that, to the best of his knowledge, the work described is original except when duly and properly acknowledged.

The work described in Chapter 7 was performed in collaboration with L.Martínez, and his co-workers; the author is responsible for the spectroscopic data and structural elucidation, not for the collection of samples or the chromatographic separations.

The work described herein has not been submitted for any other degree.

Summary

The current ideas relating to the biosynthesis of turmerones are discussed, and a biosynthetic pathway leading to α- and β-turmerones is proposed. The conformation of β-turmerone assigned by Japanese workers is shown to be based on erroneous assumptions; their data are insufficient for assignment of the absolute stereochemistry of β-turmerone. A chemical correlation to juvabione is proposed, and all current methodology is inadequate for the selective transformation of a 1,3-diene to an α,β-unsaturated methyl ester. It is shown that this transformation can be performed *via* the addition of a sulphenyl halide to the 1,3-diene. Addition of phenylsulphenyl chloride to 2,3-dimethyl-1,3-butadiene gives the 1,2-adduct: 2-chloro-2,3-dimethyl-1-(phenylthio)but-3-ene. This adduct rearranges thermally to the 1,4-adduct. The 1,2-adduct is converted into a variety of β-substituted sulphides by replacing the chloride with a suitable nucleophile: MeO^-, AcO^-, ^-CN, ^-OH. Hydride transfer to the tertiary centre is slow, and rearrangement to the 1,4-adduct is a competing process. Conversion of β-hydroxysulphides from 1,3-dienes to alkenylepoxides is achieved, and the epoxides rearrange to aldehydes by acid treatment. This constitutes an oxidative monofunctionalisation of 1,3-dienes, and similar transformations are obtained with 4,4-dimethyl-1-methylenecyclohex-2-ene, and with *trans*-penta-1,3-diene. The thermolysis of (2-hydroxy-1-phenylethyl)pyridinecobaloxime is studied by ^{1}HNMR, and employed to synthesise 1-(carboxymethyl)ethylpyridinecobaloxime. No alkylcobalt species is obtained in the reaction with dienes or unactivated olefins.

Finally, the determination of the structure of a new lignan from *Virola elongata* is described.

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List of Abbreviations

bp	boiling point
cm	centimetre
cm^{-1}	reciprocal centimetre
CI	chemical ionisation
CoA	coenzyme A
D	deuterium
DMSO	dimethylsulphoxide
DCC	N,N'-dicyclohexylcarbodiimide
e.g.	exempli gratia
EI	electron impact
Fig.	figure
g	gram(s)
GC	gas chromatography
h	hour(s)
H-ax	axial proton
H-eq	equatorial proton
HMG	3-hydroxymethylglutarate(-yl)
HPLC	high performance liquid chromatography
IR	infra-red

MHz	Megahertz
min	minute(s)
mm	millimetre(s)
mmol	millimole(s)
mol	mole(s)
m.p.	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NADP	nicotinamide phosphate
NADPH	reduced nicotinamide phosphate
nm	nanometre(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
ppm	parts per million
SET	single electron transfer (mechanism)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
UV	ultra-violet
v/v	volume-to-volume ratio
$W_{\frac{1}{2}}$	width at half height
WCOT	wall-coated open tubular

w/v	weight-to-volume ratio
w/w	weight-to-weight ratio

List of Illustrations

This work is dedicated to

my parents and all my teachers,

with deep gratitude.

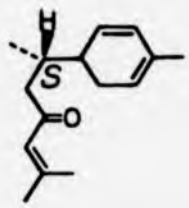
1 Introduction

1.1 Aims and Organisation of the Thesis

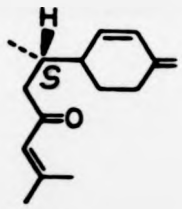
Turmeric, the dried rhizomes of Curcuma longa (Linn.), has been used as a spice and colouring substance for several millenia. It was well known in Vedic times[1], and remains in widespread use today. The main constituents of its essential oil, however, have only recently been isolated and their structure determined[2,3]. These are the turmerones: α-turmerone (1)[2], β-turmerone (2)[2] and ar-turmerone (3)[3] (but see Chapter 2). Because turmeric is cheap and plentiful, these sesquiterpenes are readily available, and would be ideal starting materials for the synthesis of a variety of related substances.

One of the main constituents of the oil, β-turmerone (2), has a trans-conjugated diene. Although this structural feature is common among readily available natural products, these have not been exploited as starting materials for the synthesis of less readily available compounds. This is mainly because of the difficulty of achieving selective mono-functionalisation of one of the double bonds of such conjugated dienes.

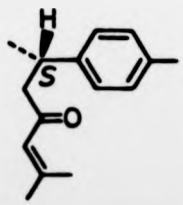
This work begins by setting the turmerones into perspective in the general context of the terpenoids, and reviewing some recent contributions to the elucidation of the biosynthesis of bisabolane sesquiterpenoids. In the second chaper, further developments in the structural and spectroscopic studies of turmerones are presented.



(1) α-Turmerone



(2) β-Turmerone



(3) ar-Turmerone

The Turmerones are the main constituents of the essential oil of Curcuma longa

The third chapter deals with the structure and reactivity of conjugated dienes, in an attempt to explain their special peculiarities in ionic reactions. No mention is made of the Diels-Alder reaction and other pericyclic reactions, as these have been substantially covered in recent literature[5-8]. This chapter will also present some of the exploratory work performed by the author, which led to the successful strategy for monofunctionalisation of 1,3-dienes.

In the fourth chapter, this successful strategy, the electrophilic addition of sulphenyl halides, is expounded and analysed. This fourth chapter constitutes the main body of the work, and contains the most important results of the research described in this thesis.

Chapter 5 is a short account of an interesting and promising side-road to the investigation: the use of cobalt-hydride species as functionalising agents, by forming covalent carbon-cobalt bonds with some olefins. This is an area under development[6], and some preliminary work is described.

In chapter 6, the experimental procedures are described.

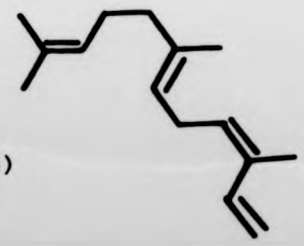
Chapter 7 presents a short coda to this study of natural products. In it, the elucidation of the structure of lignans from Virola elongata[10] is presented. This was a study in collaboration with J.C.Martinez and his group at the Universidad Nacional de Colombia, Bogota. The substances were obtained and purified by his group. Spectroscopic observations, and the structural determination were done by us at Newcastle.

1.2 Sesquiterpenes : Bisabolane and Turmerones

Terpenes are a class of compounds which arise biosynthetically from mevalonic acid, and present, in general, C_{5n} carbon atoms, where n is a whole number. Because a structural feature is an isoprene-type moiety, these compounds have been called "isoprenoids". In some terpenes, however, the simple isoprenoid structure may be difficult to discern, because a multitude of skeletal rearrangements may occur *in vivo* to generate the observed compound. Carbon atoms may be lost or added, and terpenoid moieties may be coupled to fragments derived from other biosynthetic pathways. This leads to a bewildering array of structures, which have been a source of inspiration, frustration and challenge to a host of organic chemists.

Sesquiterpenes are terpenes which contain fifteen carbons in their skeleton, i.e. arising from three such "isoprenoid" units. There are over 1,000 sesquiterpenoids known[12] and more are discovered every year[13,14].

Some sesquiterpenoids present remarkable biological activity, e.g. (Z,E)- α-farnesene (4) and (E,E)- α-farnesene (5) which are alarm pheromones of the red fire ant, *Solenopsis invicta*[15].



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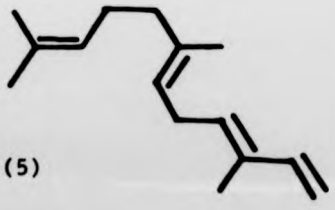
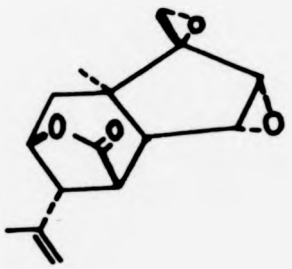


(5)

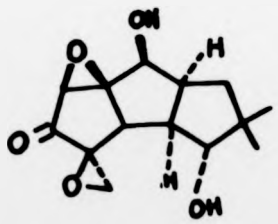
Alarm Pheromones of *Solenopsis invicta*

Some are exceedingly toxic, such as certain compounds with the picrotoxan skeleton, e.g. coriamyrtin (6), which are found in plants from the Coriaria genus, indigenous to New Zealand[16,17].



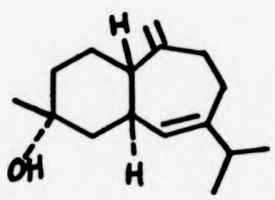
(6) coriamyrtin

Coriolin (7), a metabolite of Coriolus consors, is a powerful antibiotic which is active against gram-positive bacteria, Trichomonas, and Yoshida sarcoma cells[18-20].



(7) coriolin

It has long been cause of perplexity why the Central American leaf cutter ant ignores many of the species of plant indigenous to its habitat, but attacks mercilessly maize and other plants on which the peasant population depend for their livelihood. It was recently found[21] that some plants of the region exude sesquiterpenoids (8) - (10), which have a strong repellent effect on leaf-cutter ants, and therefore protecting from this pest the very species that generates them.



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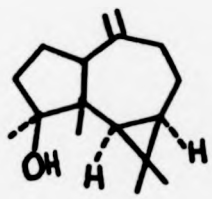

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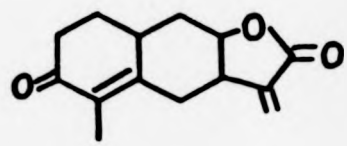
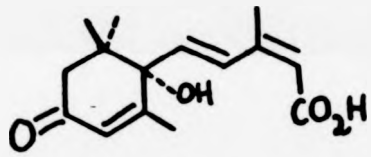


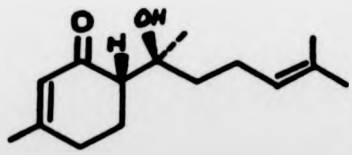
(10)

Abscissic acid[22,23](11) is ubiquitous throughout the higher plants, and as its name implies, accelerates abcission of leaves and fruit.



(11)

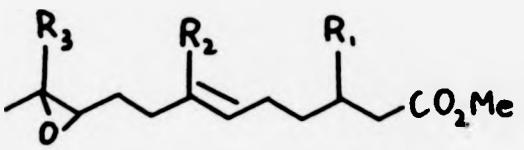
Compadre[69] and his collaborators have reported the isolation of a sesquiterpenoid (12) with a very sweet taste - making it a possible competitor in the non-nutritive sweetener business (see also ref. 79).



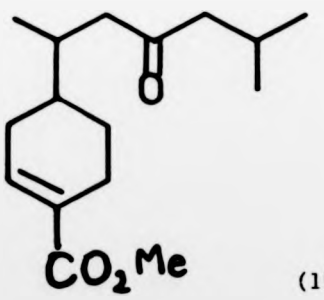
(12) Hernandulcin

Juvenile hormone[24](13) and its analogues[25-27](14), and compounds with juvenile hormone activity such as juvabione[28-32](16) modify the type of cuticle produced by an insect after moulting. If excess quantities of a compound with juvenile hormone activity

are present during moulting and while the new cuticle is generated, adult characteristics do not develop properly and the insects remain as infertile adultoids. For this reason, juvenile hormone analogues have been postulated as very specific insecticides, although these predictions have not yet borne out in practice.



(13) $R_1=R_2=R_3=C_2H_5$
(14) a) $R_1=CH_3$, $R_2=R_3=C_2H_5$
b) $R_1=R_2=CH_3$, $R_3=C_2H_5$
c) $R_1=R_2=R_3=CH_3$

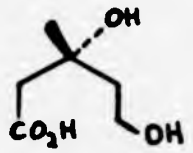


(15) Juvabione

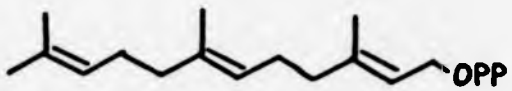
Juvabione (15) has the bisabolane skeleton in common with the turmerones (1) - (3). Numerous synthesis of juvabione and its diastereomers have appeared in the literature[33-40], but none that would compete with the economy of transforming β-turmerone, in a few steps, into juvabione. As will appear in Chapter 4, the methodology for doing so has been developed.

1.3 Biosynthesis[41]

Sesquiterpenes arise from mevalonic acid (17) via farnesyl pyrophosphate (18). The biosynthesis of acyclic sesquiterpenes is illustrated by that of farnesyl pyrophosphate (18). As shown

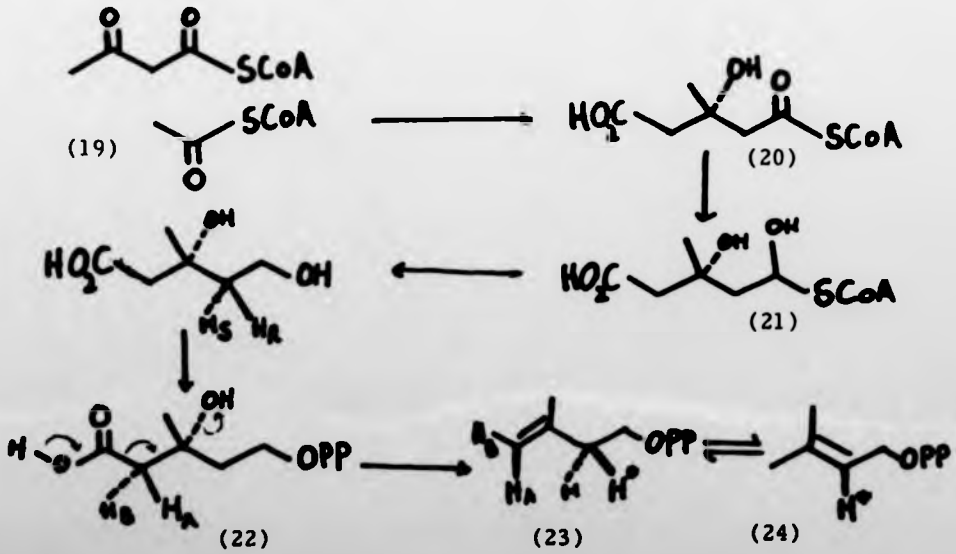


(17)

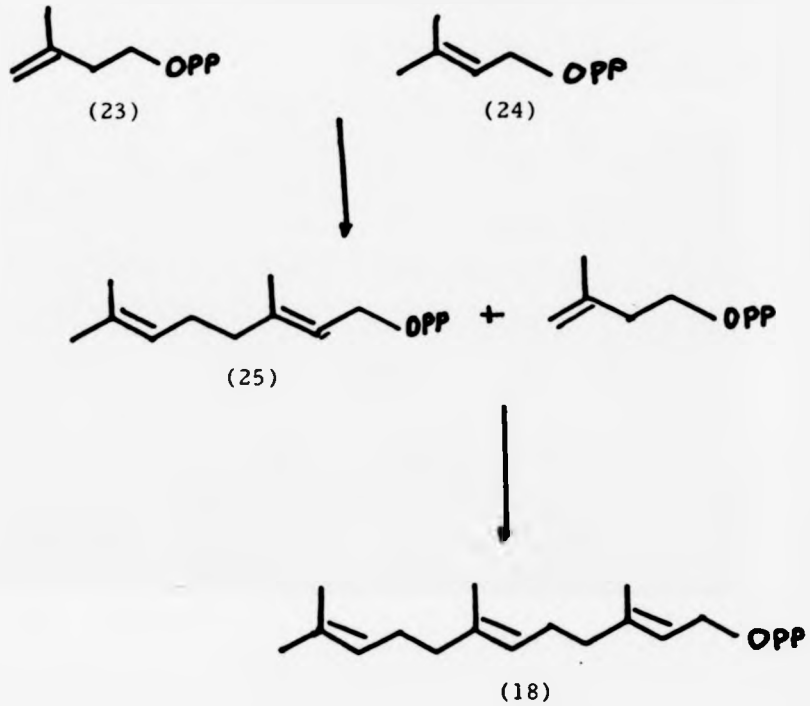


(18)

in Scheme 1.1, mevalonic acid arises from acetyl-coenzyme A via an NADPH-mediated reduction[45] of (3S)-3-hydroxy-3-methylglutaryl-CoA (20). Mevalonic acid (17), in turn, generates isopentenyl pyrophosphate (23) and dimethylallyl pyrophosphate (24), the actual building blocks of the terpenoids[43]. Dimethylallyl pyrophosphate (24) and isopentenyl pyrophosphate (23) condense to form geranyl pyrophosphate (25), which reacts with another molecule of isopentenyl pyrophosphate (23) to generate farnesyl pyrophosphate (18) (see Scheme 1.2).

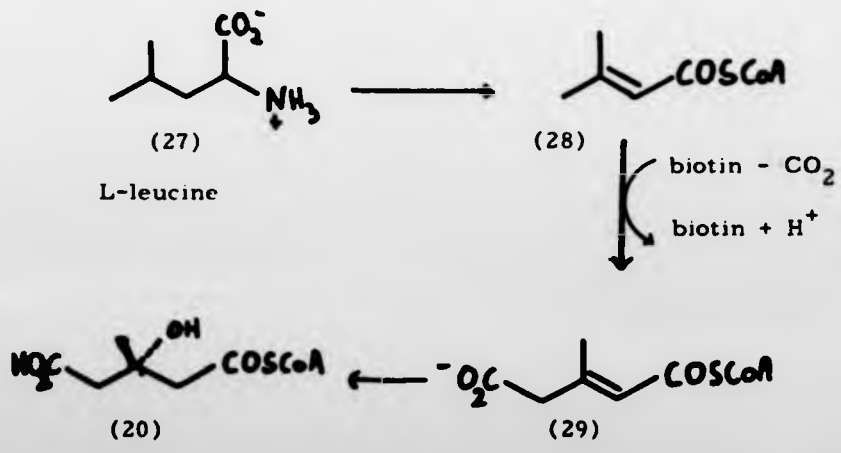


Scheme 1.1 from Herbert[44]

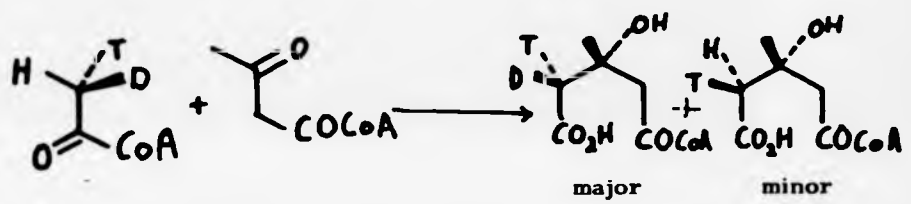


Scheme 1.2 Biosynthesis of Farnesylpyrophosphate

The intermediate (S)-3-hydroxy-3-methylglutaryl-CoA (20) can be formed from acetic acid via acetyl-CoA or from L-leucine (27) via a biotin-dependent carboxylation[46] (see Scheme 1.3).



Scheme 1.3

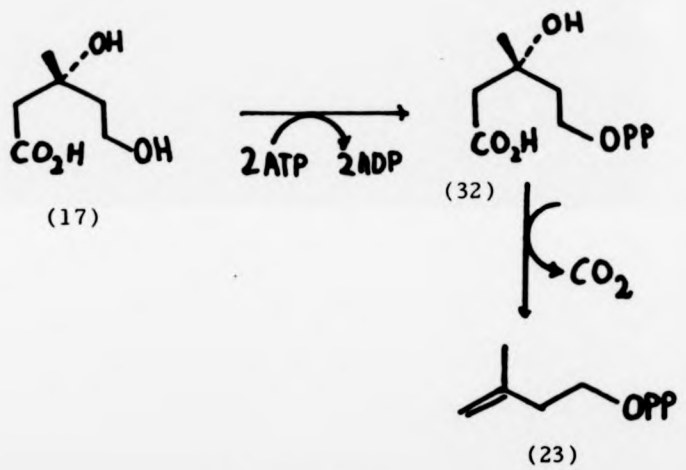


Scheme 1.5 from Torssell[50]

The pathway from L-leucine, however, is a minor one, and in some cases may involve catabolism of leucine to acetyl-CoA, before incorporation[74].

The detailed mechanism of the formation of mevalonic acid from acetyl-CoA is one of some complexity. The subtleties relate to the stereochemical course of the condensation of acetyl-CoA (19) with acetoacetyl-CoA (18) to give (S)-3-hydroxy-3-methylglutaryl-CoA (20). Does this process occur with inversion or retention of configuration at the methyl group of acetyl-CoA? That is to say, assuming deprotonation of this methyl group by an enzymic base to yield an intermediate, resonance-stabilised carbanion, does this species react with acetoacetyl-CoA on the same face as that from which the proton was removed (retention pathway) or on the opposite face (inversion pathway)?

This was solved by some elegant work involving chiral methyl groups. (R)- and (S)-acetic acids were prepared[47,48] and condensed to their corresponding CoA esters. The condensation to 3-hydroxy-3-methylglutaryl-CoA proceeded with inversion of configuration and a normal hydrogen isotope effect[49], as shown on Scheme 1.5. Addition to the carbonyl occurs exclusively at the Re face, giving rise to (S)-3-hyroxy-3-methylglutaryl-CoA. The mechanism, then, is that of an enzymatic Claisen condensation, in which the enolate of acetyl-CoA retains its configuration. To explain the overall stereochemistry there must be precise positioning by the enzyme of a basic group (to generate the enolate from bound acetyl-CoA) and an acidic group of the enzyme that protonates the carbonyl oxygen of acetylacetyl-CoA[51]. It should be noted that recent



(17) (32) (23)

Scheme 1.6

studies of Claisen condensations indicate that a single-electron transfer mechanism (SET) may operate in certain cases, although perhaps is unimportant in aliphatic substrates[68].

The next step, the reduction of (3S)-3-hydroxymethylglutaryl-CoA (20) is mediated by HMG-CoA reductase, and involves a transfer of hydride from the pro-4R-position of the dihydropyridine ring of NADPH[55-57], generating the (3S)-mono-thioacetal (21) which is further reduced to (3R)-mevalonic acid (17). The hydrogen atom that is transferred in this second reduction appears in the 5-pro-S position of the resulting mevalonic acid[52,53].

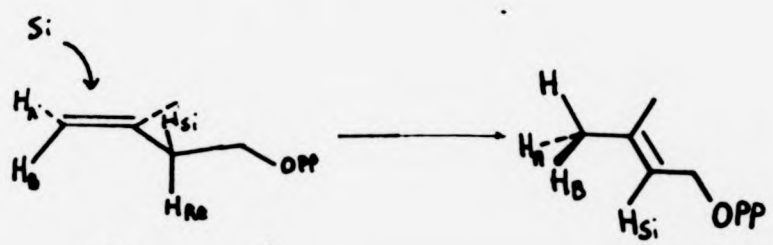
The conversion of (3R)-mevalonic acid (17) into isopentenyl-pyrophosphate (23) involves the action of three enzymes[54]. Mevalonate kinase initially phosphorylates (R)-mevalonic acid to generate (R)-5-phosphomevalonate (31). Another kinase, 5-phosphomevalonate kinase, phosphorylates (31) to give (R)-5-pyrophosphomevalonate (32), which is decarboxylated by the action of a pyrophosphate decarboxylase to generate isopentenyl pyrophosphate (23). This is illustrated in Scheme 1.6.

The phosphorylations are apparently straightforward, although the question arises as to whether the phosphate moiety is transferred *via* an enzyme-phosphate complex, and therefore, with double inversion (retention) of stereochemistry at phosphorus[58,59].

The decarboxylative elimination of (32) to (23) has been shown[60] to proceed in an *anti*-fashion, and therefore it might be concerted, as shown in Scheme 1.7. However, although the

2R$_1$3R-(32) (23)

Scheme 1.7



(23) (24)

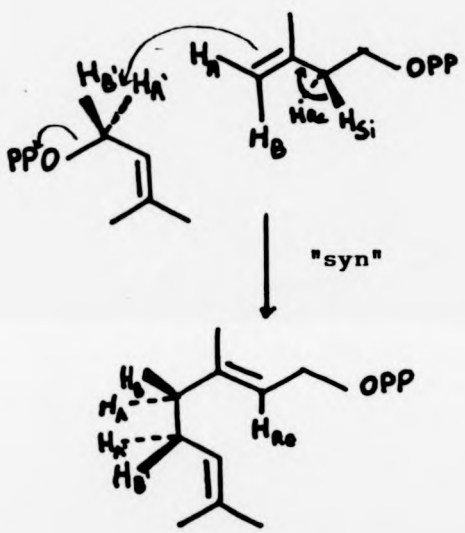
Scheme 1.8

stereochemistry of the elimination is anti, whether the hydroxyl group is phosphorylated prior to, or concomitantly with, the decarboxylation, has not been established.

The following step is an enzyme-mediated, reversible isomerisation of isopentenyl pyrophosphate (23) into dimethylallyl pyrophosphate (24) (cf. Scheme 1.1). In this process a methyl group is generated in a trans relationship to the methylene phosphate moiety.

There is, as shown in Scheme 1.8, an anti- relationship between the proton added to the double bond (on the Si-face) and that removed from the 2-position (H-Re).

The isoprenyl building blocks are ready to be assembled, and this is done by enzymes called prenyl transferases. Initially, geranyl pyrophosphate (25) is generated (cf. Scheme 1.2) by the coupling of isopentenyl pyrophosphate (23) and dimethylallyl pyrophosphate (24). The stereochemistry of this reaction has been elucidated by Cornforth[64,60] during his studies on the biosynthesis of steroids. The reaction is a formal alkylation in which the pyrophosphate group of dimethylallyl pyrophosphate (24) is replaced with inversion of configuration, by isopentenyl pyrophosphate (23) (cf. Scheme 1.9). The reaction is a syn process, and it has been proposed that it is stepwise. Poulter and his co-workers[70-71] have studied the reactions of farnesyl pyrophosphate synthetase, and in particular, the 1'-4 condensation between isopentenyl pyrophosphate (23) and dimethylallyl pyrophosphate (24) or geranyl pyrophosphate (25). They established that the condensation reactions are electrophilic[72] and have three main phases: a) an elimination

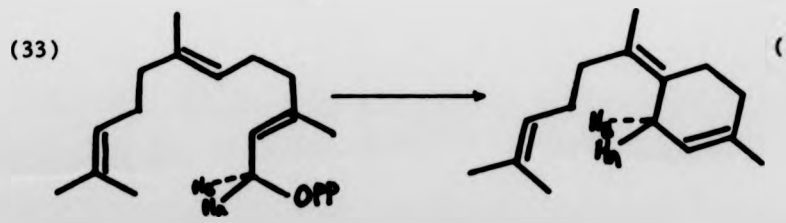


Scheme 1.9

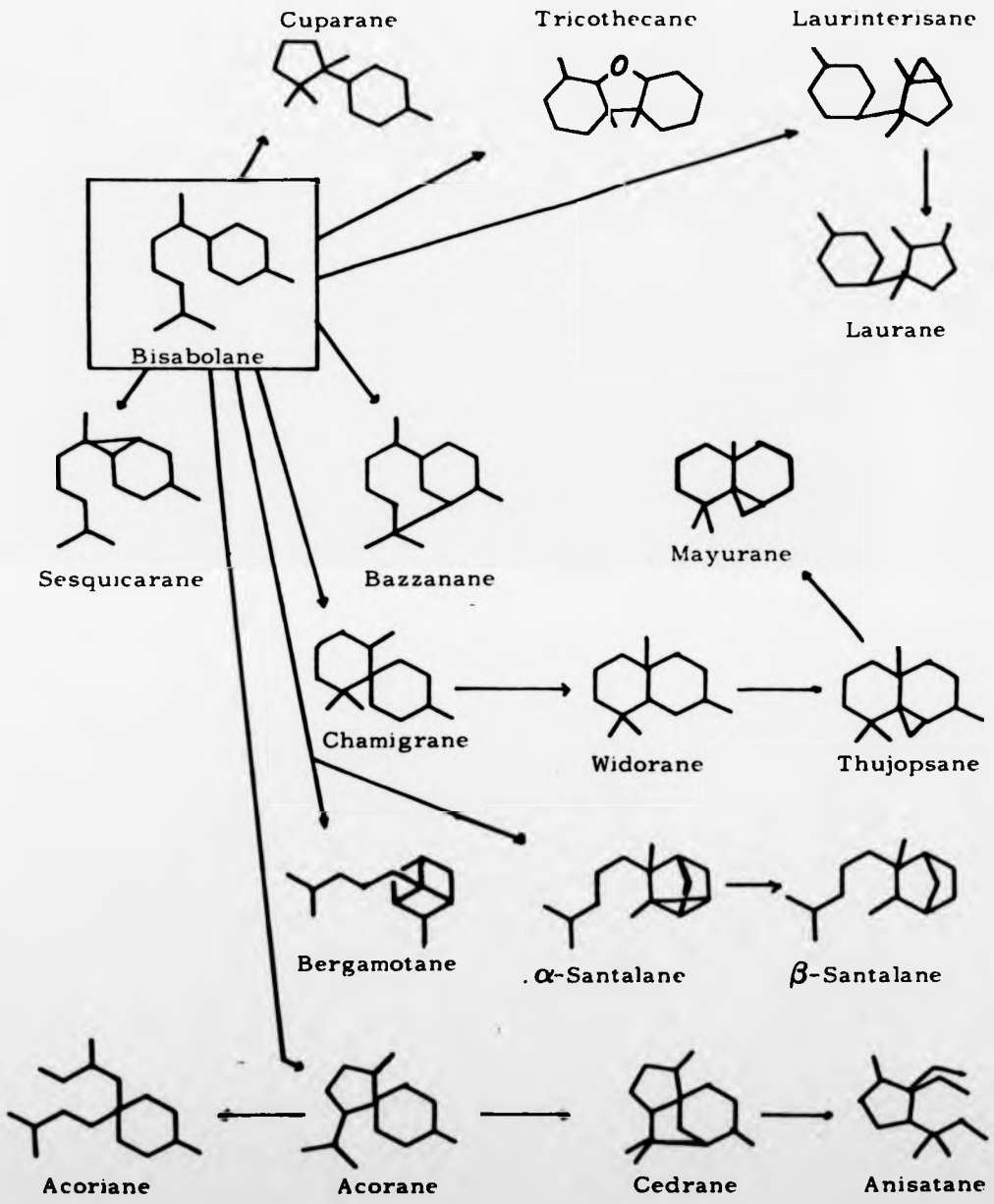
of the 1' pyrophosphate, generating a cationic species that is b) attacked by the double bond of isopentenyl pyrophosphate (23) generating a new cationic species from which c) a proton is eliminated. The intermediate cationic species does not lose stereochemical integrity because it is present as a tightly bound ion pair at the enzyme's active site. The ion pair is then attacked by the double bond of isopentenyl pyrophosphate (23). Be that as it may, the remarkable stereocontrol exerted during this process has been exploited for stereospecific C-C bond formation in the enzyme-aided synthesis of about 30 homologues of farnesyl pyrophosphate[73].

The process described above is the biosynthesis of (2E,6E)-farnesyl pyrophosphate (17). Many prenyl transferases generate this stereochemistry about the double bonds[67], as is the case of two geranyl transferases isolated from Ricinus communis[65]. For the biosynthesis of cyclic sesquiterpenes, however, isomerization about the 2-double bond must occur before cyclisation can take place.

It has been shown that a cell-free enzymic system of Andrographis paniculata transforms (E,E)-[1,1-$^{3}H_2$;12,13-$^{14}C_2$]farnesyl pyrophosphate (33) into (Z)- γ-bisabolene (34) without loss of tritium (cf. Scheme 1.10)[66].



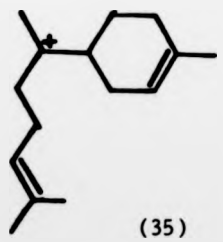
Scheme 1.10



Scheme 1.11 Structural relationship of Some Sesquiterpenes

An interesting point is that the same cell free system[75] transforms (E,E)-[1,1-$^3H_2$]farnesol into (Z,E)-[1-^3H]farnesol with loss of the pro-S hydrogen and retention of the pro-R hydrogen at the 1-position. These observations indicate the presence of two independent enzyme systems, an (E,E)-farnesyl pyrophosphate isomerase[75] and an (E,E)-farnesyl pyrophosphate isomerase-cyclase[66]. The detailed mechanism of the cyclisation has not been elucidated, although there is a large amount of information about labelled compounds that are incorporated into sesquiterpene skeletons[76,78].

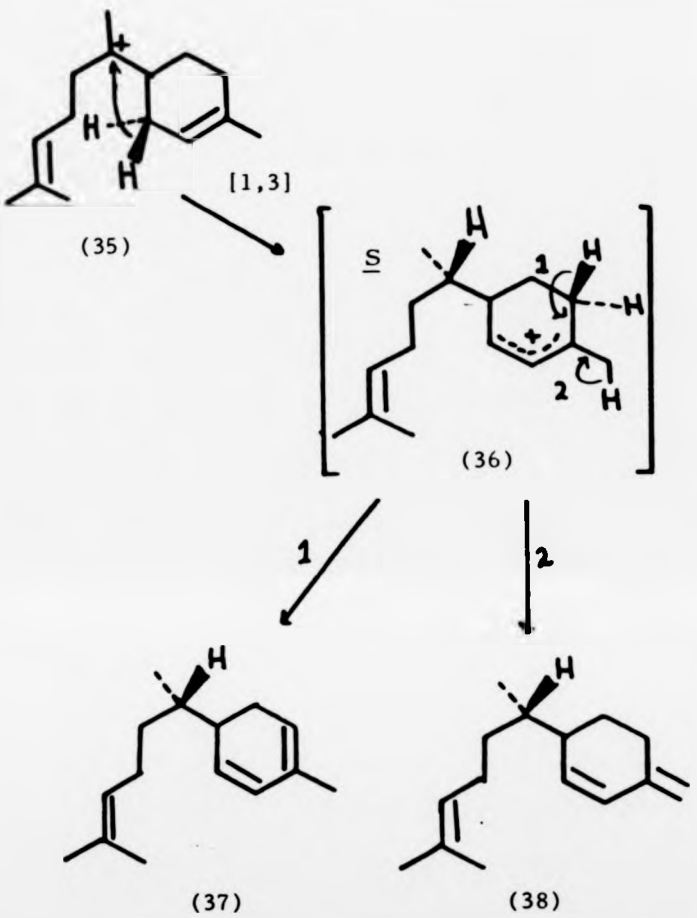
γ-Bisabolene (34) is one of the most widely distributed sesquiterpenes. In Scheme 1.11, the structural relationship between several skeletal types of sesquiterpenoids is illustrated. In view of this relationship, a central role has been proposed for the immediate precursor to bisabolene. Thus, the bisabolyl cation (35), via sigmatropic hydrogen shifts and Wagner-Meerwein type skeletal



(35)

rearrangements, gives rise to a great number of the sesquiterpenoid structural types. Attractive though this proposal may be, confirmatory evidence is lacking.

Biosynthesis of the turmerones presumably follows the same course as that of γ-bisabolene (34). However, when the cyclisation of farnesyl pyrophosphate generates the bisabolyl cation (35),



Scheme 1.12

a [1,3]-prototropic shift generates an allylic endocyclic cation (36) which can lose a proton either at the 6-position of the ring, or at the 7-methyl group to generate the corresponding sesquiterpenes (37) and (38). Both have been reported to be constituents of the oil of turmeric[81].

Studies of the oil by GC/MS indicate the presence of substances with m/z 202 and 204 (see Fig. 1.13)[82]. It is proposed that these precursors are acted upon by a monooxygenase, which generates an alcohol. Sesquiterpenoid alcohols related to the turmerones have also been reported as constituents of the oil, even if their precise structure was not elucidated[83].

This mono-oxygenase may be akin to those responsible for ω-oxidation of fatty acids, and we predict that the source of oxygen is bound atmospheric dioxygen. These intermediate alcohols may then be oxidised by a dehydrogenase to generate α- and β-turmerones which are further oxidised to generate ar-turmerone. The oxidation of α- and β-turmerones to ar-turmerone may be non-enzymic, as is indicated by the degradation of isolated samples of turmerones and of the oil of turmeric, whose content of ar-turmerone increases with storage. It might be necessary to follow this biosynthetic pathway in detail before asserting, like Govindarajan[80] does, that ar-turmerone is not an artifact of the isolation procedure.

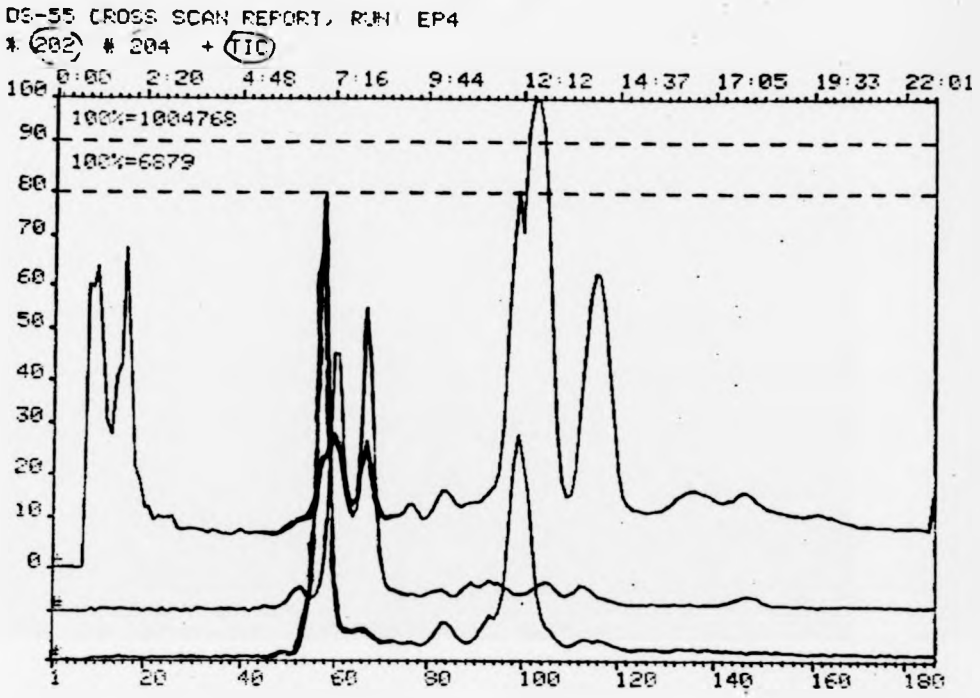


Figure 1.13

Figure 1.13, GC/MS trace of a fraction from chromatography of oil of turmeric. The trace shows total ion current (TIC), and single-ion monitoring at m/z 204 and 202, vs. retention time. The peaks appearing between 50 and 70 min correspond to desoxy analogues of the turmerones, which appear between 90 and 120 min (cf. Ref.1).

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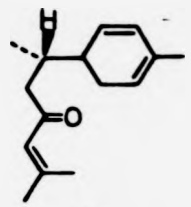
2. Recent Studies on the Constituents of the Oil of Turmeric

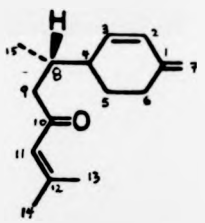
2.1 The Structural Problems

The essential oil of turmeric (Curcuma longa Linn.) constitutes 3-6% of the dry weight of the rhizomes. Its detailed composition varies with the particular cultivars[1], conditions and time of storage of the rhizomes, and the method of extraction. We found that when dry turmeric rhizomes (Allepey fingers) were freshly ground with solid CO_2, and extracted immediately with cold petroleum spirit (b.p. 40-60°C), the oil contained three main components. When subjected to GC/MS analysis, two of these components presented m/z = 218, and the other one had m/z = 216. Preparative gas chromatography was not successful for isolating the substances of m/z 218, only the compound with m/z = 216 being sufficiently stable to be obtained by this technique. This was shown to be ar-turmerone[3] (3). The other two compounds, which together composed ca 60% of the fresh essential oil (cf. Ref. 1, p65) could only be separated by laborious column chromatography followed by HPLC, when it was essential to add 1% triethylamine to the eluant to inhibit acid-catalysed degradations. The structures of these compounds were deduced from their spectroscopic data. High resolution mass spectrometry indicated that both compounds possessed the elemental composition $C_{15}H_{22}O$. The 400 MHz ^{1}HNMR spectra of the compounds, with selective decoupling, provided evidence about the connectivity of the carbon skeleton. From these data, the structures (1) and (2) were assigned for the compounds, which were named α-turmerone and β-turmerone, respectively, in analogy to α- and β-phellandrene, the corresponding monoterpenoids.



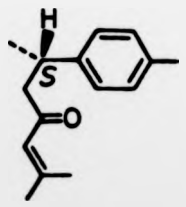
(1)

α-Turmerone



(2)

β-Turmerone



(3)

ar-Turmerone

Figure 2.1 The Turmerones

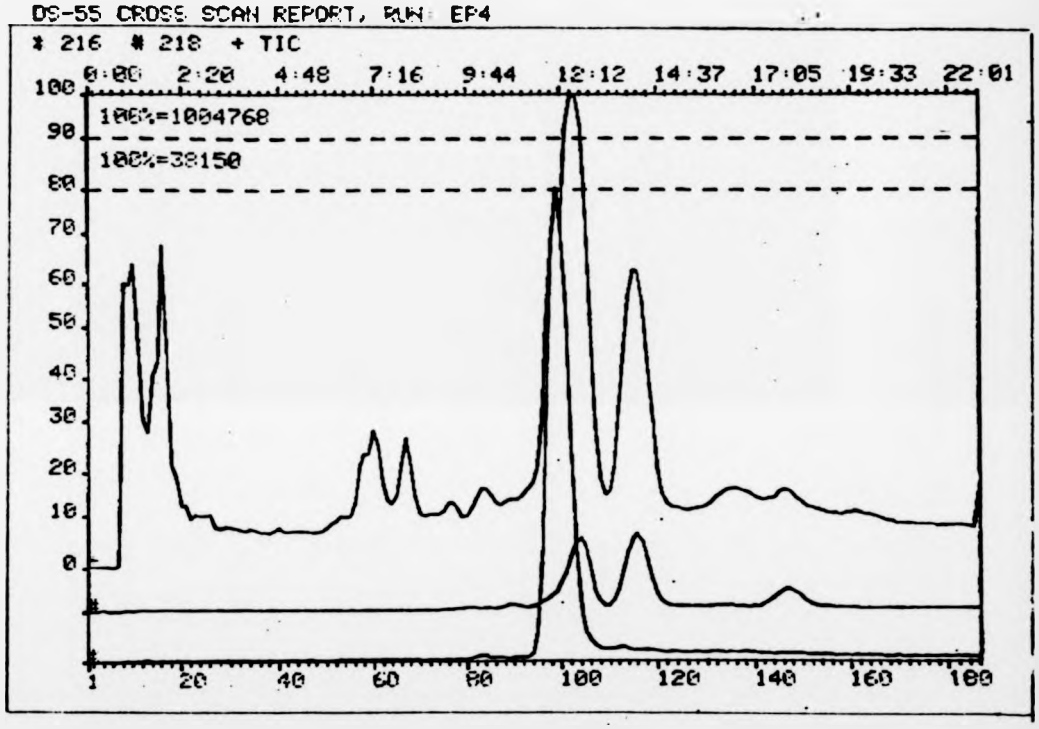
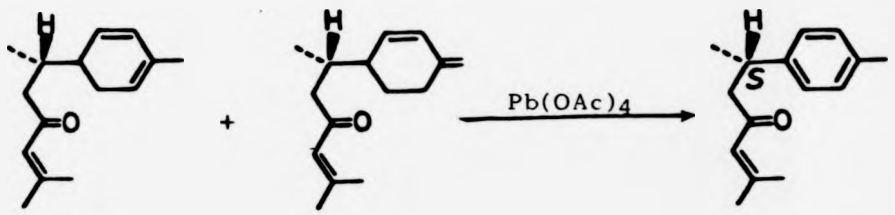


Figure 2.2 GC/MS trace of turmeric oil. The peak with m/z 216 corresponds to ar-turmerone. α- and β-turmerones appear with m/z 218. Single-ion monitoring allows resolution of two superimposed peaks.

The configuration at C-8 of both α- and β-turmerones is S, because a mixture of turmerones was oxidised by lead tetraacetate to the known (S)-ar-turmerone[4]. The configuration

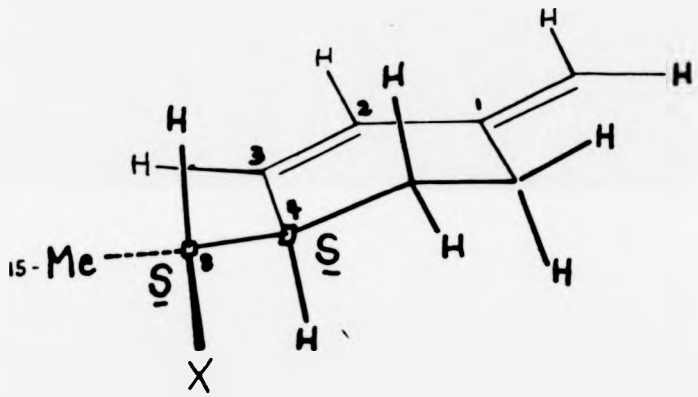


(1) (2) (3)

Figure 2.3 Oxidation of α- and β-turmerones to ar-turmerone

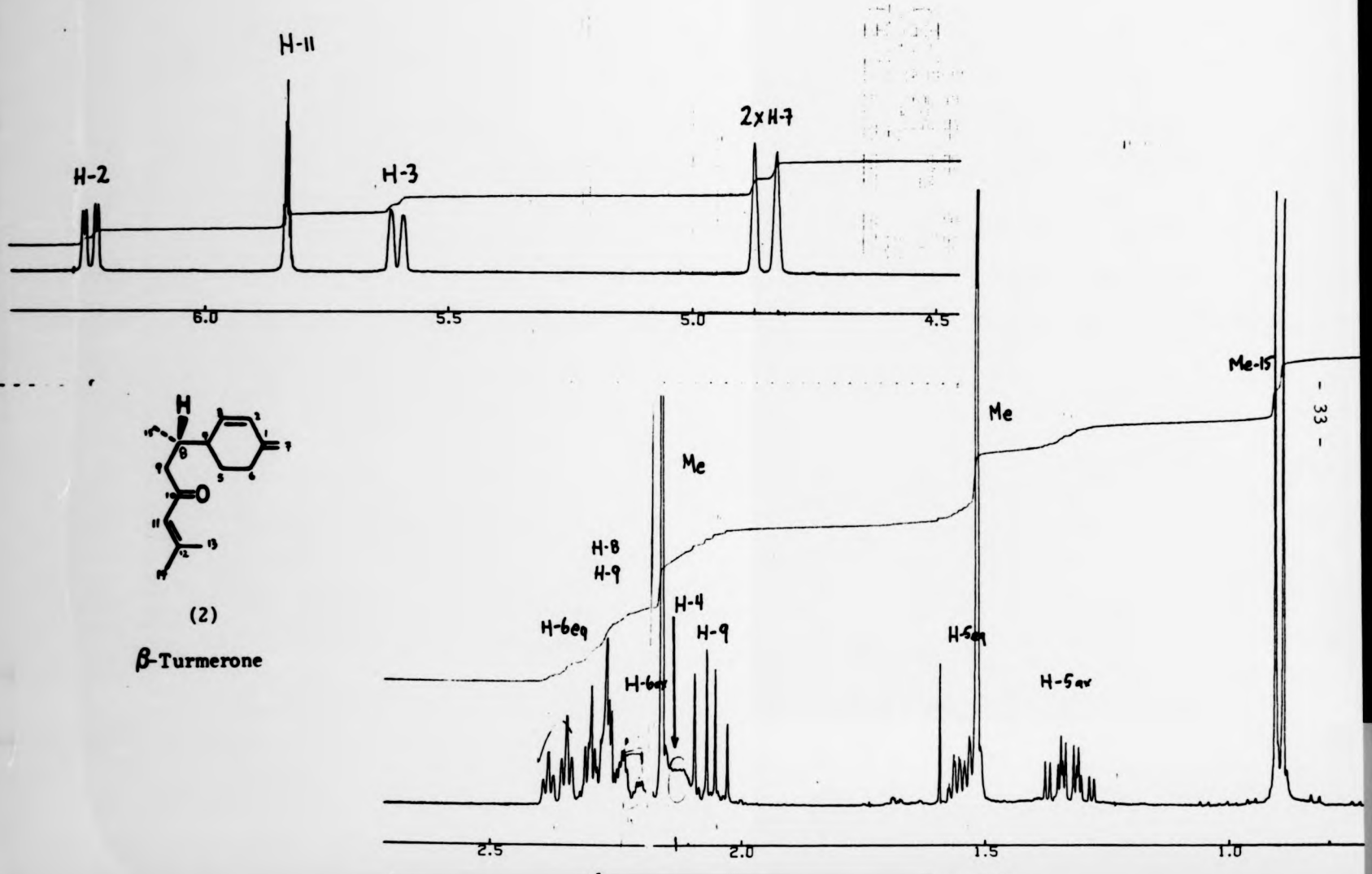
of the corresponding chiral centres at C-4 has not been determined. Full details of the structure determinations for α- and β-turmerones were given in the author's M.Sc. thesis and a preliminary account has been published[3] (see Appendix 3).

Hikino and his collaborators, in a paper[5] submitted three months after ours had appeared in print, and published after the author's M.Sc. thesis, claimed to have isolated a "novel" sesquiterpenoid from the Japanese drug "udon" (Curcuma longa, Linn. = turmeric!). The structure of this "novel" sesquiterpenoid was identical to that we had found for β-turmerone! They did, however, assign the stereochemistry at C-4 as S. Their argument is based on the observation of an intramolecular NOE between the Methyl-15 and H-3 (δ=5.67 ppm in $CDCl_3$), and the assumption that the hydrogens at C-4 and C-8 adopt the "thermodynamically most stable anti-arrangement". Their argument is not convincing, for several reasons which became apparent



X = $CH_2COCH=C(CH_2)_2$

Figure 2.4 Hikino's proposed conformation for the C-4 - C-8 bond. NOE between Me-15 and H-3 implies S configuration at C-4. For clarity's sake, the sidechain is represented by X in the conformational diagrams that follow.



(2)

β-Turmerone

Figure 2.5 400MHz ^{1}HNMR spectrum of β-Turmerone in C_6D_6

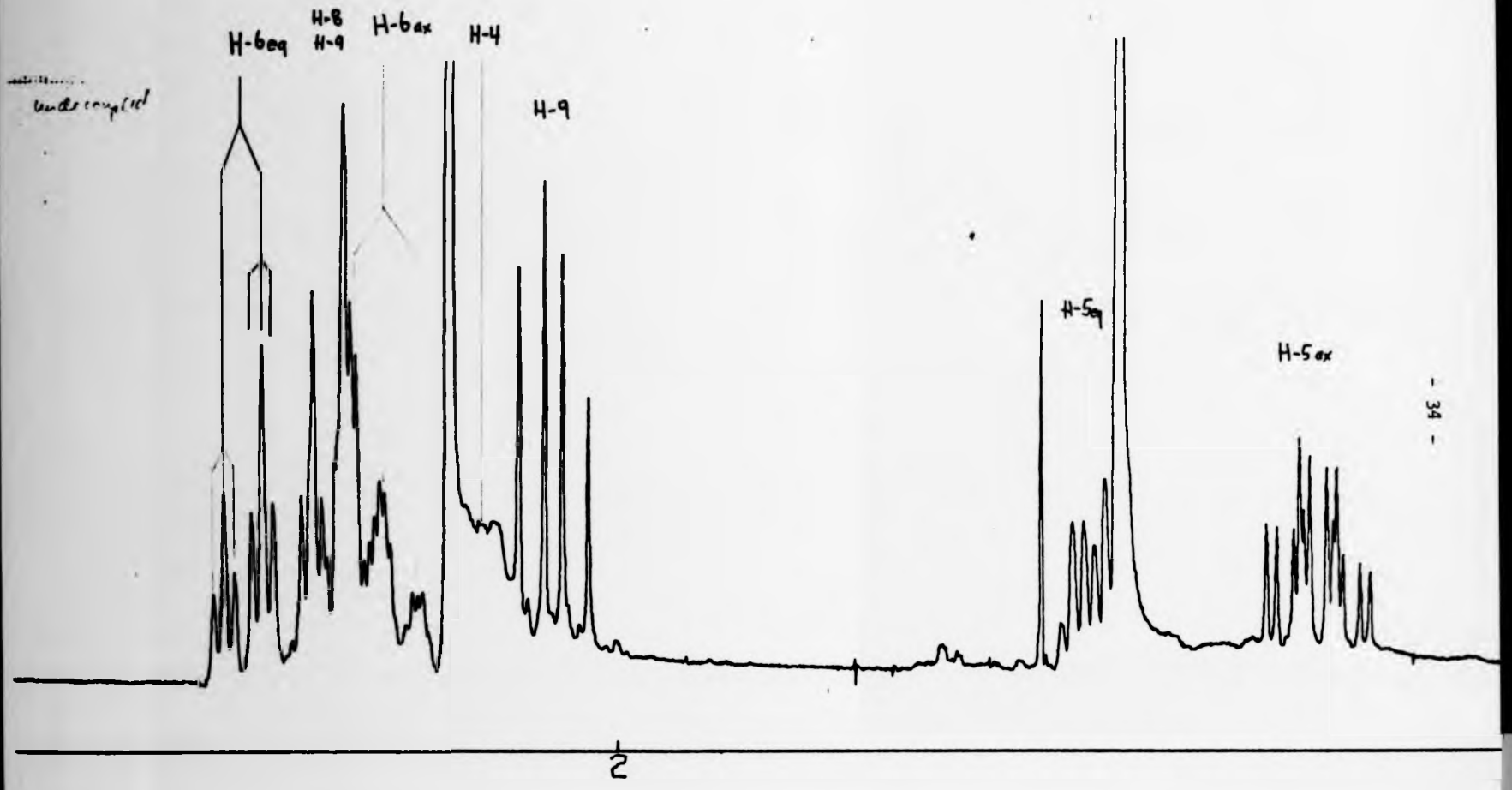


Figure 2.6 Detail of Figure 2.5

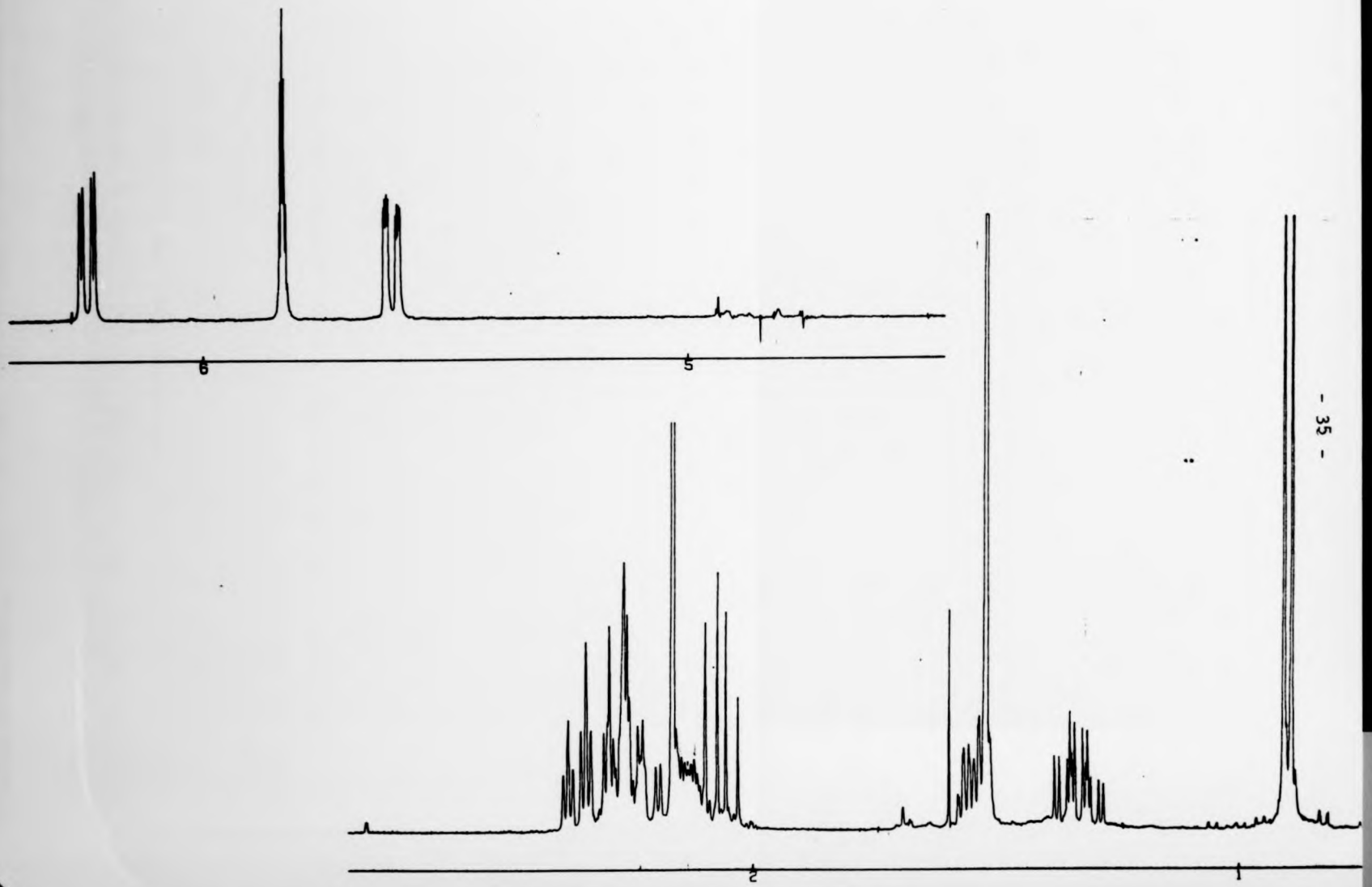


Figure 2.7 Irradiation at 4.84ppm

when we re-examined the spectroscopic evidence that was accumulated during the author's M.Sc. work. A more detailed analysis of the spectral evidence was deemed necessary, and is presented here.

The 400 MHz ^{1}HNMR spectrum of β-turmerone in $CDCl_3$ was difficult to tackle because of the coincidence of many resonances in the area 2-2.5ppm. By using C_6D_6 some resonances were shifted, and it was easier to interpret the spectrum with the help of double resonance experiments.

The undecoupled ^{1}HNMR spectrum in C_6D_6 is shown in Fig.2.5, together with the spectral assignments. The gross structure is readily appreciated. The 1-proton septet ($\underline{J}$=1.2Hz) at 5.83ppm is coupled to two 3-proton signals at 2.16 and 1.51ppm. The broad 1-proton singlets at 4.87 and 4.82ppm, together with the double multiplets at 6.24 (1H) and 5.61ppm (1H) indicate that the ring is as shown. In a double-resonance experiment, strong irradiation at 4.84ppm removed small couplings from these doublets, and that at 6.24ppm was simplified to a double doublet, J=10 and 2Hz; that at 5.61ppm showed a coupling of 10Hz and 3 small (<1Hz) couplings (see Fig.2.7). Two small, but significant, changes were also observed in the high-field region: a simplification of the multiplets at δ=2.23, and the removal of some couplings of the absorption at δ=2.13, made it appear as a complex double multiplet, rather than as a broad, featureless absorption. This indicates that these correspond to axial protons, because π-contributions to allylic coupling constants are larger when the angle θ is 0° or 180°[6,7] (see Fig.2.8). These absorptions correspond to H-6ax

and H-4. Irradiation of the absorption at 1.37ppm caused substantial

Figure 2.8 Conformational dependence of allylic couplings[7]

sharpening of that corresponding to H-4, the signal for H-6ax was simplified, and the double triplet at δ=2.36 collapsed to a double doublet, J=8 and 2Hz; the absorption at δ=1.55 became a broad singlet (see Fig.2.9). This indicates that the proton resonating at δ=1.37 is in a trans-diaxial relationship to H-4 and H-6ax, and must therefore correspond to H-5ax, whilst the absorption at δ=2.36 is due to H-6eq. These assignments were confirmed by the observation of complementary changes in the spectrum upon irradiation at 1.55ppm; only a very small coupling was removed from H-4, whilst a 2Hz coupling was removed from H-6eq (2.36ppm) and the multiplets corresponding to H-6ax were sharpened up, due to the loss of a small coupling. The signal at 1.55ppm is due to H-5eq.

Summarizing the situation so far, we have assigned H-4, H-5eq, H-5ax, H-6eq and H-6ax, and have shown that H-4 is an axial proton. The conformation of the ring that satisfies these constraints is a half-chair, with the side chain in a pseudo-equatorial position.

Having identified the protons in the ring, it remains to assign those absorptions due to the side-chain. Irradiation at 0.86ppm, i.e. Me-15, caused simplification of the region 2.35-2.4ppm

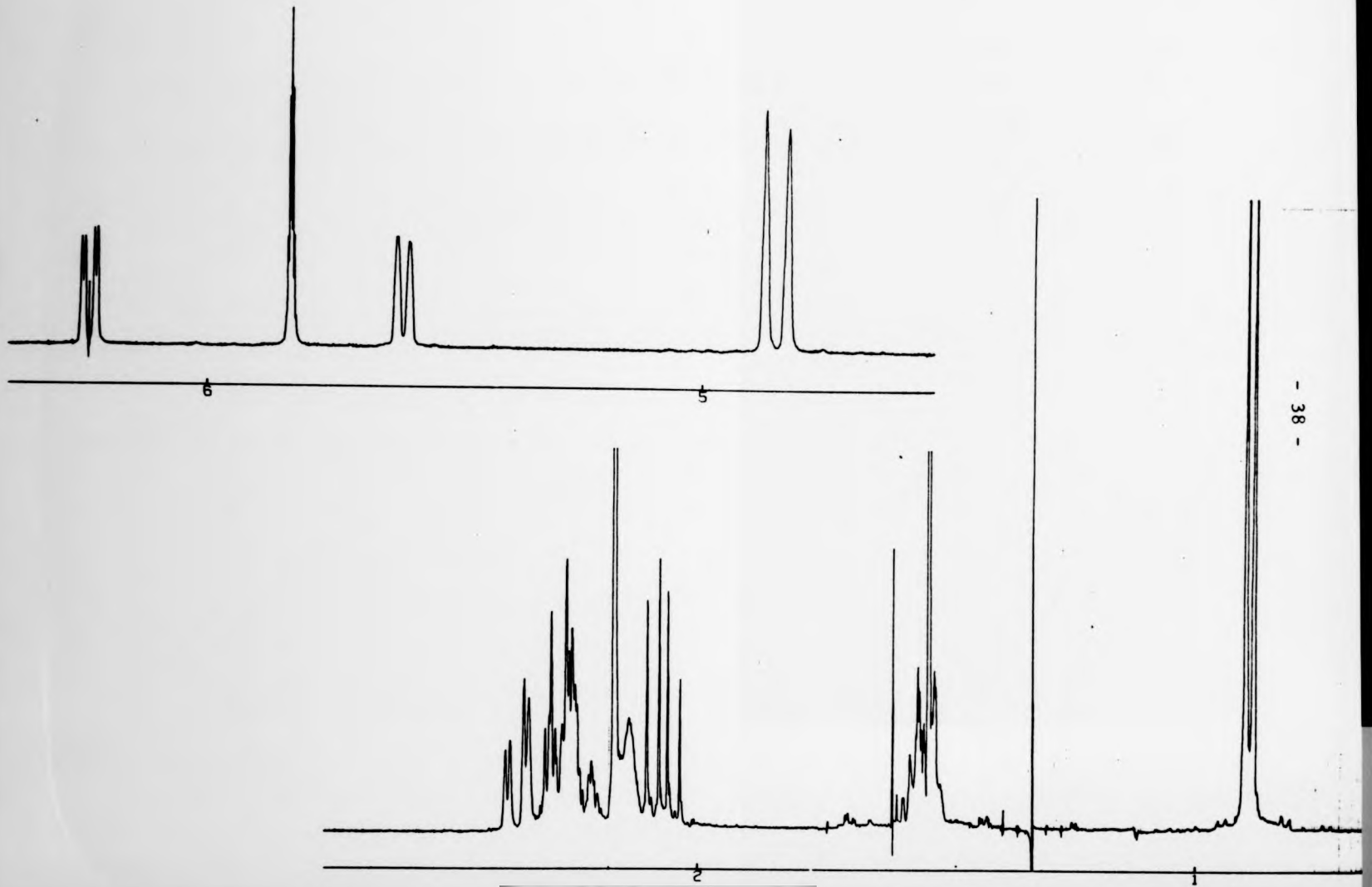


Figure 2.9 Irradiation at 1.37

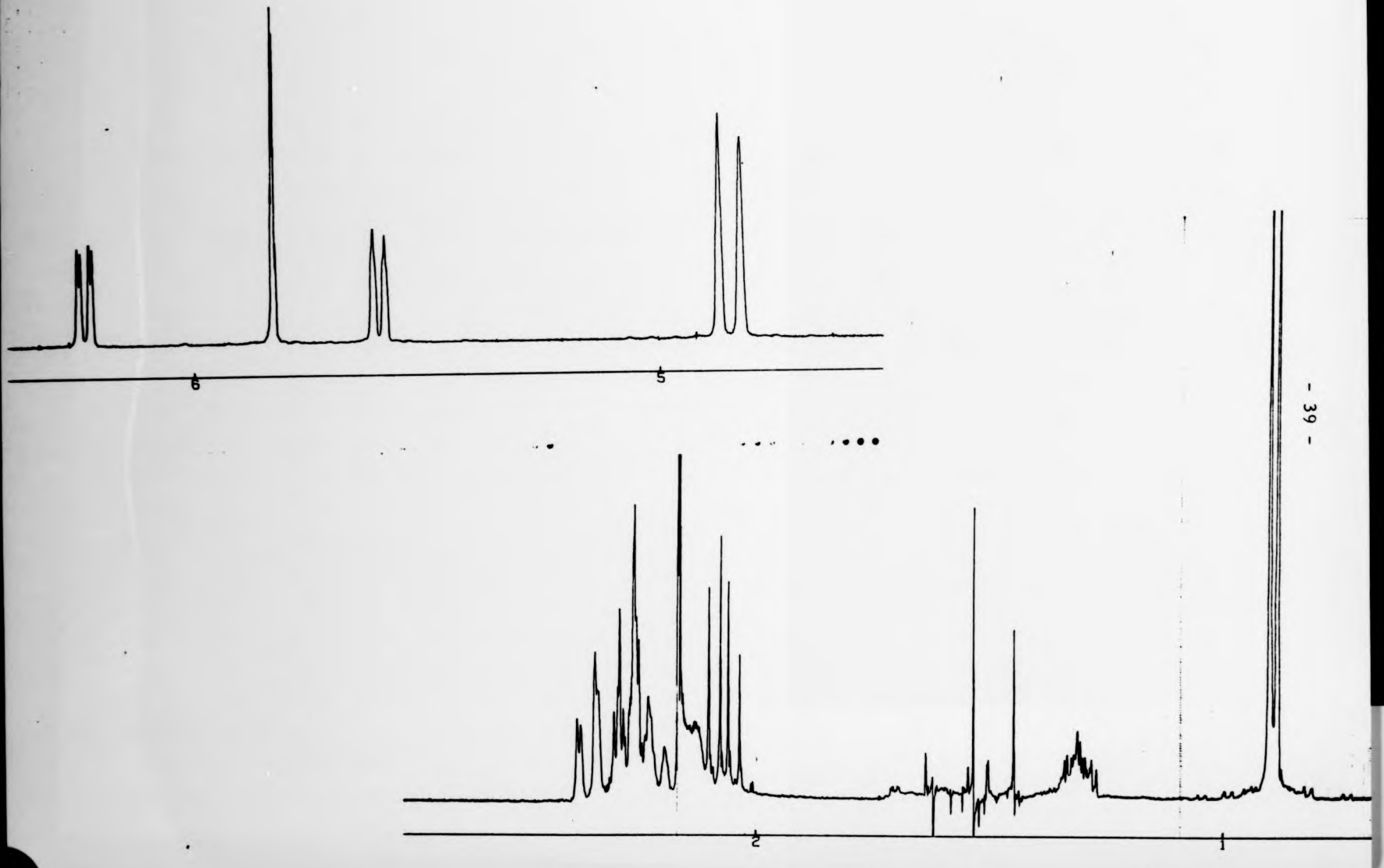


Figure 2.10 Irradiation at 1.55

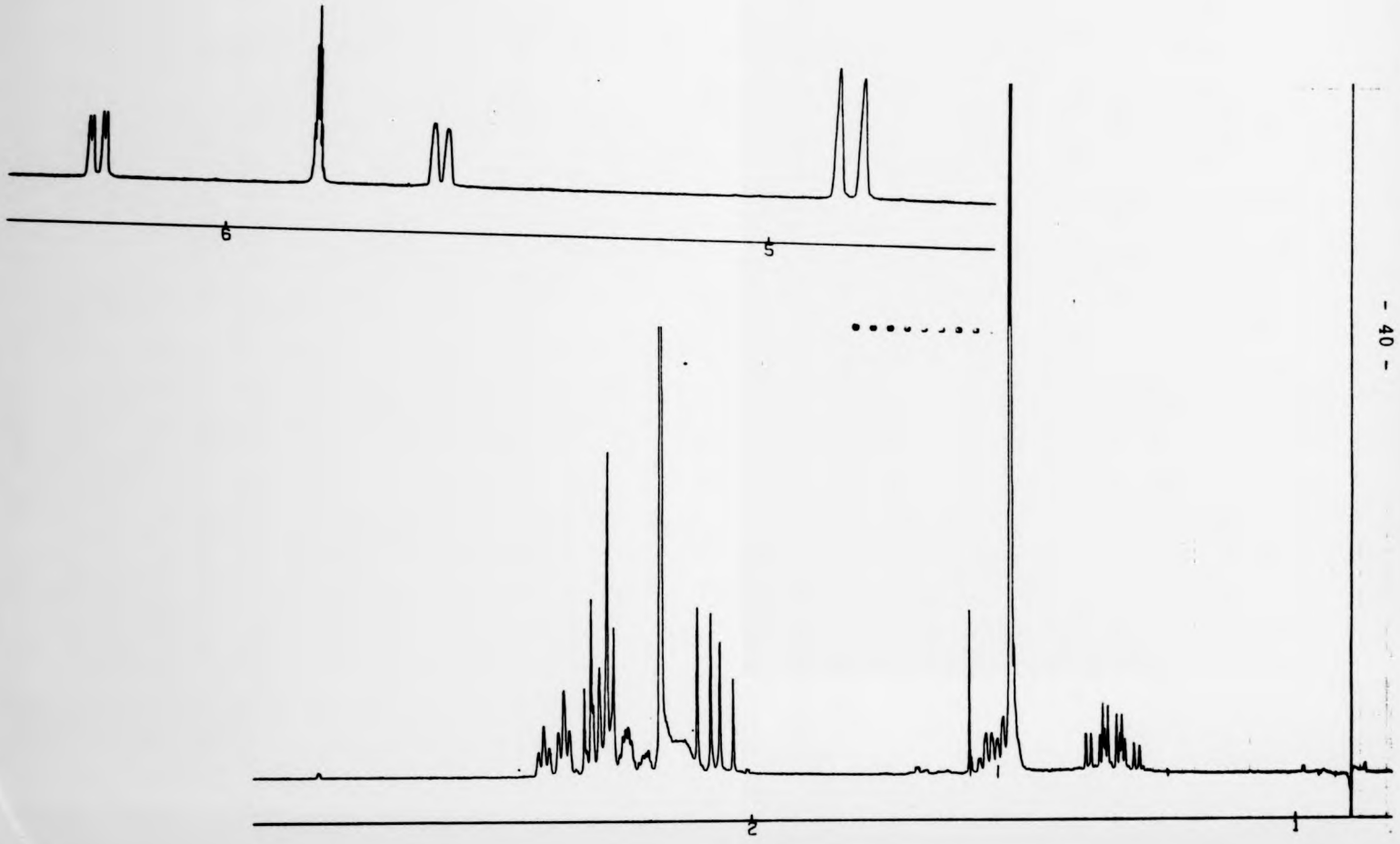


Figure 2.11 Irradiation at Me-15, 0.86ppm

(see Fig.2,11). This simplification is not sufficient for detailed analysis of this region, which is due to the strongly coupled absorptions of one of the H-9 protons and H-8. The double doublet at 2.06ppm is due to H-9', and presents coupling constants of 9 and 5Hz. These are the geminal coupling constant to H-9, and the vicinal one, to H-8. We have thus assigned all the resonances in the spectrum, and come to the crux of our argument.

Hikino claims that the dihedral angle between H-8 and H-4 is near 180°, that is, they are in an anti-arrangement. If that were so, the coupling constant between these protons should be of the order of 7-10Hz[8]. As can be seen in Fig.2.9, irradiating at H-5ax caused H-4 to appear as a broad singlet. Although this singlet is not fully resolved from the methyl absorption, a coupling of 7-10Hz would be clearly observable; the coupling of H-4 to H-8 must therefore be **small** (<2Hz). Accordingly, the dihedral angle between these protons is about 90°.

These observations, of course, only demonstrate that the conformation of β-turmerone in C_6D_6 is not that predicted by our Japanese colleagues. What happens then, in $CDCl_3$?

In Fig.2.12 the ^{1}HNMR spectrum of β-turmerone in $CDCl_3$ is illustrated. The absorptions for H-5ax (1.36ppm) and H-5eq (1.71ppm) are immediately obvious, as they are identical to those observed in C_6D_6, although they appear at slightly different chemical shifts, and thus H-5eq is completely resolved from the methyl absorption at 1.56ppm. This indicates that the ring conformation

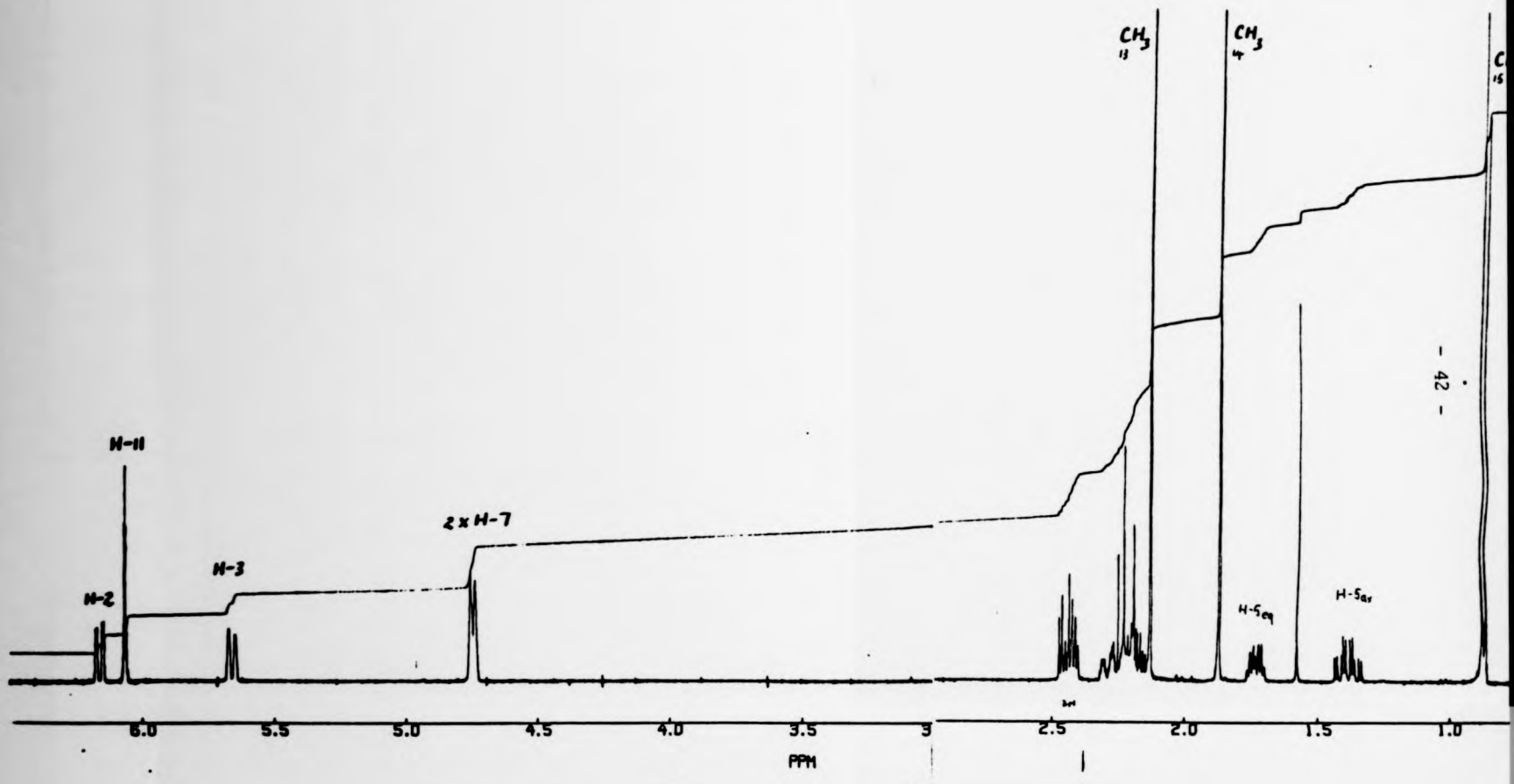


Figure 2.12 The 400MHz ^{1}HNMR spectrum of -Turmerone in $CDCl_3$

is identical in $CDCl_3$ to that in C_6D_6, i.e. the H-4 occupies an axial position, and the side chain is pseudoequatorial.

When the sample is irradiated at Me-15 (0.83ppm) in a double resonance experiment, there is considerable simplification of the absorptions between 2.1 and 2.2ppm (see Fig.2.13 and 2.14). However, because of the strong coupling effects in that region, first order analysis of the spectrum is not possible. We cannot determine the coupling constant between H-8 and H-4 from this spectrum.

Difference NOE experiments that we performed in $CDCl_3$ were not very conclusive. However, irradiation at Me-15 gave enhancements at 2.2 and 5.68ppm, although the difference spectrum is very noisy at 2.2ppm. We can be certain, however, that some effect is observed at 5.68ppm, and that corresponds to the H-3 - Me-15 interaction which was observed by Hikino. In C_6D_6, when Me-15 of β-turmerone was irradiated, enhancements of signal intensity were observed for H-9, H-9', H-3 and to a small extent, to H-5ax.

To explain these enhancements, Me-15 must be placed in sufficient proximity to H-5ax and H-3. Assuming that the ring conformation of β-turmerone is a half-chair (this is also supported by calculations using Allinger's MM2(82) force field - see below), and the dihedral angle between H-8 and H-4 is close to 90°, then only one conformation satisfies these constraints: that with the Me-15 on the opposite side of the ring to H-4. The observed

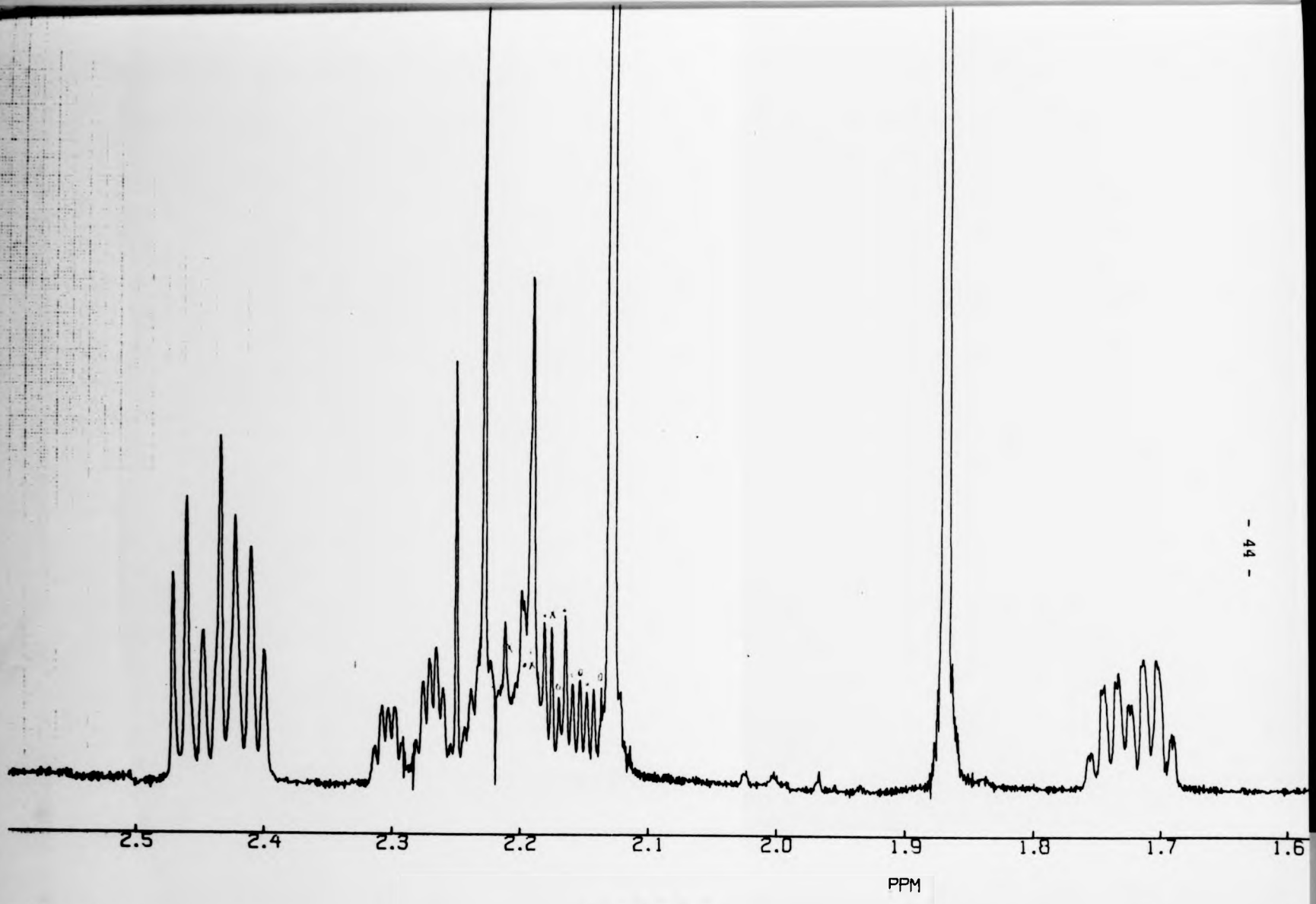


Figure 2.13 β-Turmerone in $CDCl_3$, irradiated at 6.15

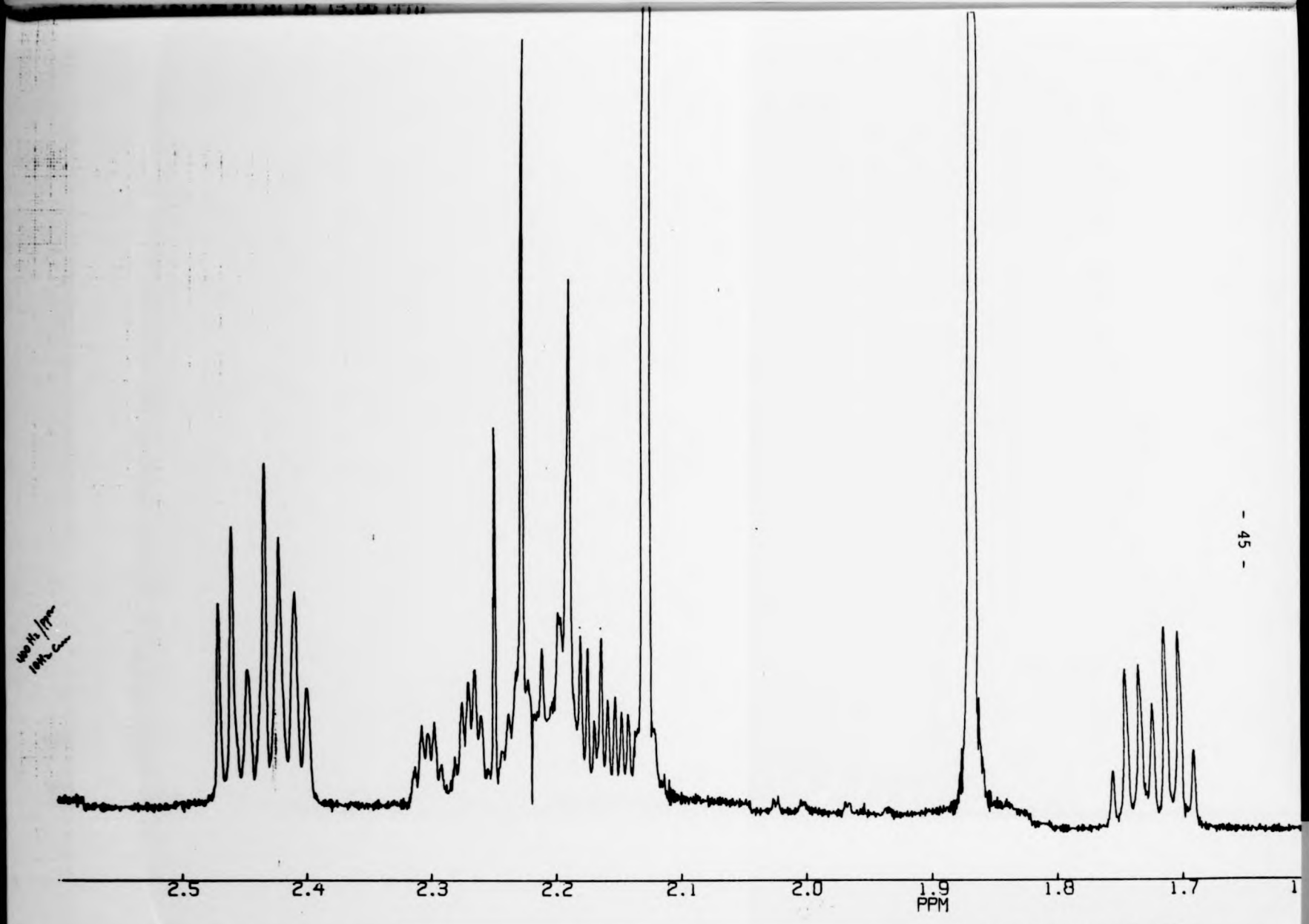


Figure 2.13a β-Turmerone in $CDCl_3$, irradiated at 5.66ppm

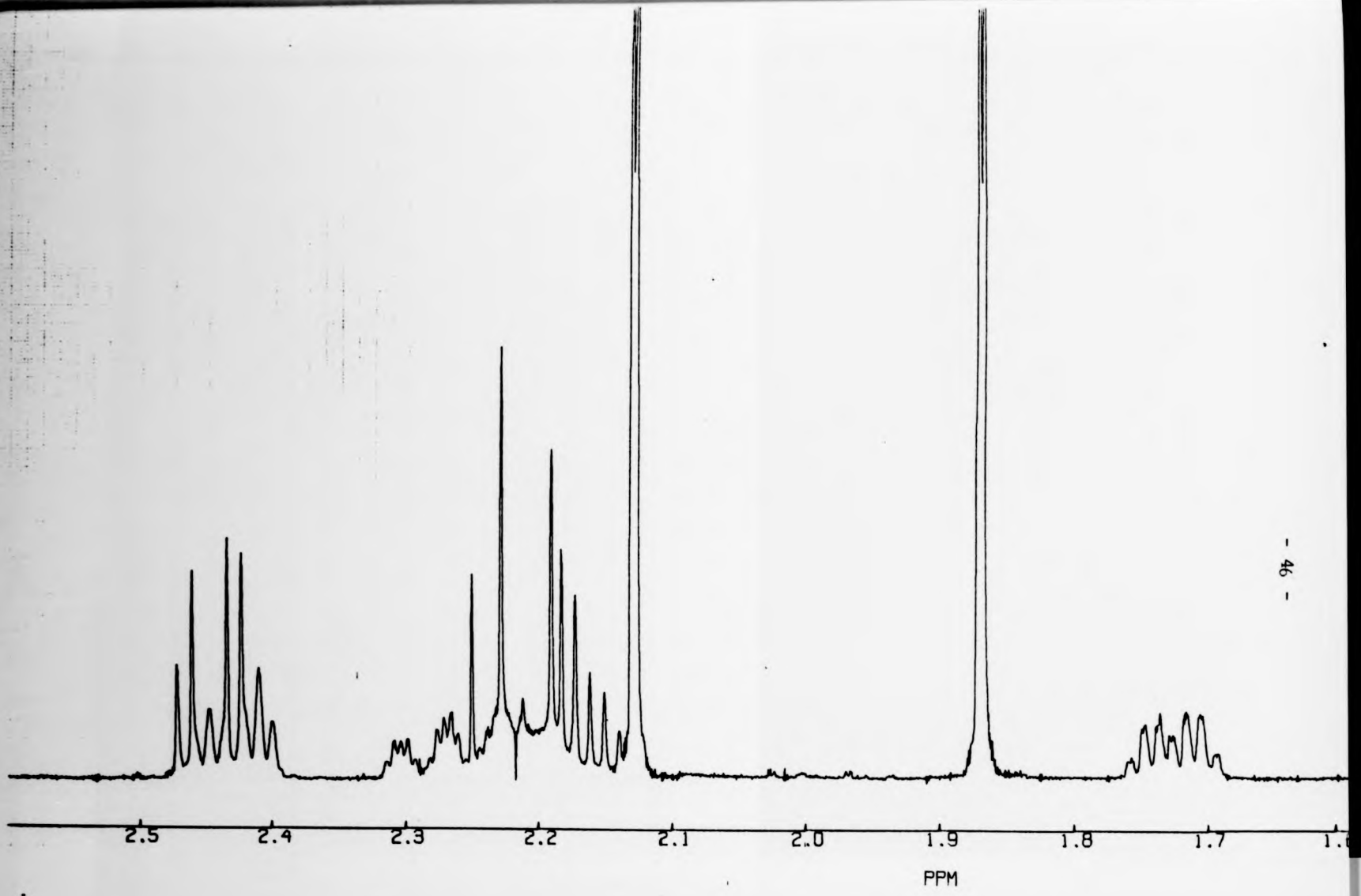


Figure 2.14 β-Turmerone in $CDCl_3$, irradiated at 0.83 (Me-15)

spectroscopic data can be satisfied by either an R, or an S configuration at C-4, as shown in Fig.2.15.

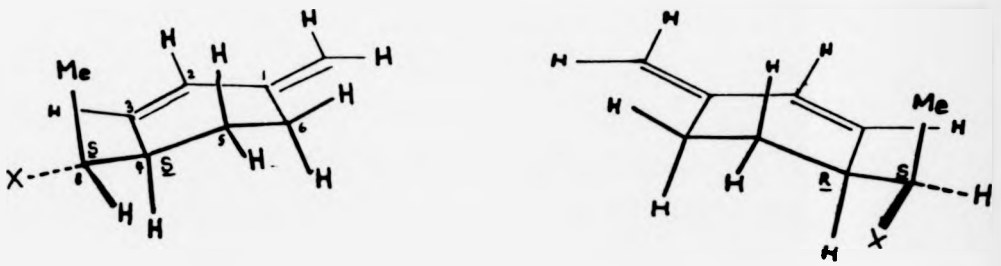


Figure 2.15

In both diastereoisomers the dihedral angle between H-8 and H-4 can be close to 90°.

To explore this further, preliminary studies of the conformational space of β-phellandrene, as a model for β-turmerone, were made using E.K.Davies' simplified molecular mechanics program (see Appendix 1). The isopropyl moiety of β-phellandrene may occupy either a pseudoaxial or a pseudoequatorial position (fig.2.16). The pseudoequatorial substitution is energetically favourable and of the three gauche conformations of the C-4 - C-8 bond, that with a dihedral angle of 81° between H-4 and H-8 is lowest in energy. This is in agreement with experimental evidence. First, conjugated dienes tend to adopt essentially planar conformations[9-11], although in 1,3-cyclohexadienes total planarity is not achieved, and the helicity of the diene moiety gives rise to a Cotton effect[12-14]. Compounds with a methylenecyclohex-2-ene moiety can also present a Cotton effect when the helicity is induced by conformational constraints, as is the case of 3-methylenecholest-4-ene[15]. The

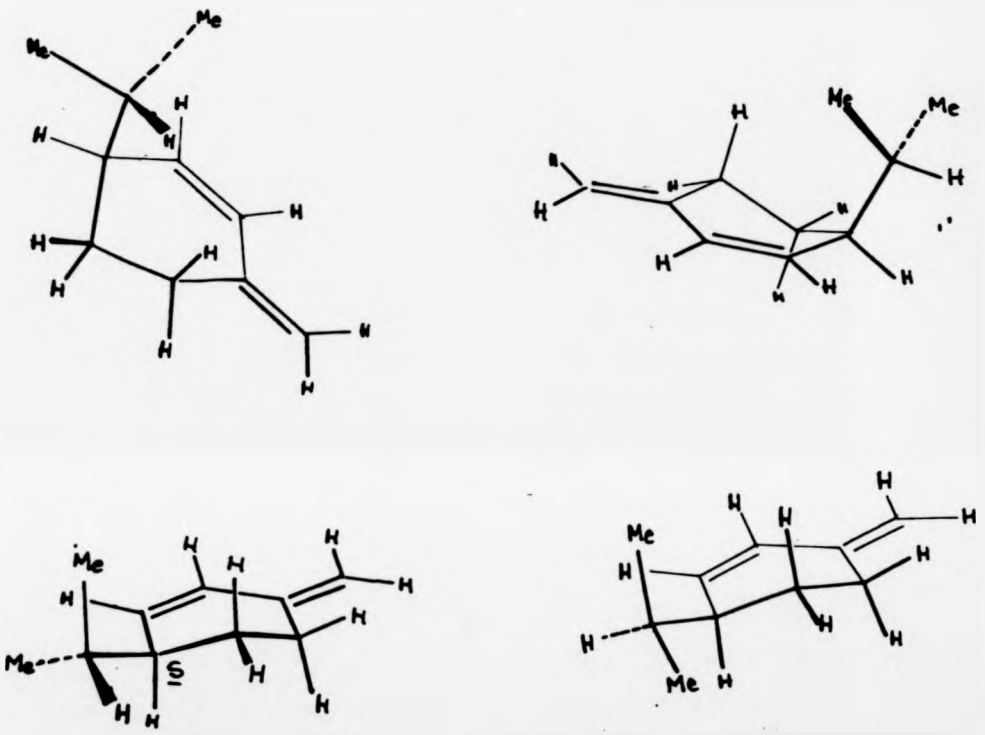


Figure 2.16 Pseudoaxial (top) and pseudoequatorial (bottom) conformations of β-phellandrene

barrier to ring inversion in cyclohexene is small ca. 22.18kJ.mol.$^{-1}$ at -164°C[16,17], but from studies of model compounds it has been suggested that the axial position for an isopropyl moiety in a 3-isopropyl cyclohexene is very unfavourable[18] compared to a methyl group. Conformational studies on cyclohex-2en-1-one[19-22] show that the lowest energy conformation has all atoms except C-5 in one plane, and the barrier to ring inversion[23] is 43.51kJ.mol.$^{-1}$. In 3-methylenecyclohex-1-ene[24,25], the barrier to ring inversion is 25.23kJ.mol.$^{-1}$. The barrier to inversion is lower than that for the ketone; this is consistent with a reduced degree of conjugation of the endocyclic double bond with the exocyclic methylene, as compared to the more polar carbonyl. In 1,3-cyclohexadiene, the barrier to ring inversion[26] is near 12.55kJ.mol.$^{-1}$. For isopropyl substituted cyclohexanes, the difference in free energy between axial and equatorial conformers[27] is 8.996kJ.mol.$^{-1}$, and for methyl cyclohexane[27] this difference is 7.11kJ.mol.$^{-1}$. In 3-methyl cyclohexene[28] the free energy difference is 3.35-4.06kJ.mol.$^{-1}$. This shows that the axial conformer is less destabilised when a double bond is present in the ring, presumably by diminishing 1,3-diaxial interactions across the ring, as well as gauche H-H interactions in the ring[30].

In the case of (-)-(R)- α-phellandrene, it has been determined that the equatorial conformer is more stable than the axial by 1.92kJ.mol.$^{-1}$, by studies of the temperature dependence of product ratios for photochemical electrocyclic ring opening[31]. Other values for the difference in stability of the equatorial and axial conformer have been reported in the literature[13,32,33], ranging between 1.05 and 3.97kJ.mol.$^{-1}$, but it seems now accepted that the lower value of 1.05kJ.mol.$^{-1}$ is the most accurate. It is in agreement

with the value of 0.818kJ.mol.^{1} calculated by Rauk and Peoples[34], who employed a minimal basis set SCF on molecular mechanics optimised conformers of β-phellandrene. By comparing the values of the barriers to inversion of cyclohexa-1,3-diene (12.55kJ.mol.$^{-1}$) and 3-methylenecyclohex-1-ene (25.23kJ.mol.$^{-1}$) we may assume that the value of the barrier in β-phellandrene will be larger than that for α-phellandrene, and it is reasonable to expect that the equatorial conformer will be preferred over the axial one. The lowest energy conformation for β-phellandrene will therefore present five near-coplanar atoms in the ring, and C-5 of the ring out of the plane, as shown in Fig.2.16. In this ring conformation, the isopropyl group must adopt a gauche conformation in which the H-3 is close to the plane bisecting the methyl groups, as illustrated. Any other gauche conformation is disfavoured by the interactions between the methyl groups and H-3, H-5ax and H-5eq.

β-Turmerone was then studied using Allinger's MM2(82) force field (see Appendix 1). The asymmetry at C-8 of the side chain of β-turmerone, as opposed to the symmetry of the isopropyl group of β-phellandrene makes for a larger difference between the energies of the gauche conformations at C-8 - C-4. The relative configuration of both chiral centres determines the minimum energy conformation. This is shown for (S,S)- β-turmerone (see fig.A1.3.6): the dihedral angle between H-4 and H-8 is 72° in the minimum energy conformation. This would correspond to a coupling constant of less than 1Hz. For the (R,S)-diastereoisomer, at the energy minimum the corresponding dihedral angle is 59°. This would also generate a small coupling constant, so

assignment of the absolute stereochemistry cannot be performed by extrapolation from the observed coupling constant.

We may therefore conclude that our Japanese colleagues were not justified in assigning the absolute configuration of β-turmerone at C-4 as S. Not only were their observations of intramolecular NOE effects incomplete, and their assignments of the ^{1}HNMR spectra insufficient, but also their assumptions regarding stereochemistry were wrong. We cannot, however, assign the stereochemistry from our spectral data. This assignment must wait until sufficient evidence is collected. In any case, our Japanese colleagues may have some of Emil Fischer's luck, and be right - after all, they have a 50% chance!

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3 1,3-Dienes

3.1 The Problems Stated

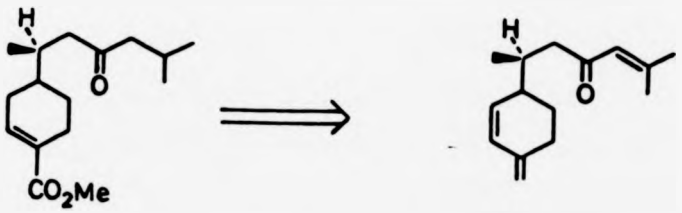
The previous two chapters set the context for our research: the structure of the turmerones had been determined, but the absolute configuration at C-4 was still unknown. As assignment of the stereochemistry at C-4 based on the spectroscopic data was not possible, so it was decided to attempt a chemical correlation.

As discussed in Chapter 1, to solve the question for β-turmerone, the chosen target molecule was juvabione. Not only was it an inherently interesting substance, and all of its diastereomers had been rigorously characterised, but also the minimal disruption of the carbon framework and the apparent simplicity of the necessary transformations made it especially attractive.

The synthetic strategy to transform β-turmerone into the corresponding diastereoisomer of juvabione was reduced to solving two main problems: a selective reduction of the double bond of the enone, and an oxidative monofunctionalisation of the methylene terminus of the ring. The first objective was reached in a comparably short time, with a copper(I)-catalysed lithium aluminium hydride reduction of the enone, in near-quantitative yield. This was reported in the author's M.Sc. thesis[1].

The tactics proposed in the author's thesis for the attainment of the second objective involved hydroboration/oxidation followed by oxidation of the resulting alcohol to the corresponding acid.

This acid would then be esterified by standard methodology, and isomerised to juvabione by treatment with base (see Fig.3.1).



juvabione β-Turmerone

Figure 3.1

This scheme proved to be impracticable in the light of further experience, and was perhaps imbued with an excess of wishful thinking. The 1,3-diene of β-turmerone could neither be efficiently mono-functionalised by those tactics nor by a number of other tactics attempted. These initial attempts to solve the problem of selective mono-functionalisation of 1,3-diene gave us an insight into the peculiar nature of conjugated double bonds, which finally led to a solution. The answer to this problem will have to wait until Chapter 4, where the successful methodology is detailed. In what remains of this chapter we shall explore the peculiarities of conjugated double bonds and discuss the results of our preliminary explorations.

3.2 1,3-Dienes, Conjugation and Delocalisation

In the first decade of this century, Brühl[2,3] observed that the molecular refractivity of conjugated dienes presented anomalies with respect to analogous unsaturated compounds where the double bonds were not in conjugation. The values of molecular refractivity

for these conjugated compounds were higher than could be expected from the simple summation of the effect of each unsaturated bond. Heats of combustion of terpenes with conjugated double bonds were lower than those for their isomers with non-conjugated olefinic linkages[4,5]. It was observations such as these that prompted chemists to propose an interaction between double bonds when they are juxtaposed. The nature and extent of this interaction has been the subject of much dispute[8,9] among theoretical chemists, but it has been a challenge to any bonding theory to explain why "irregularities" arise when bonds are conjugated.

The structure of 1,3-butadiene has been studied extensively. The equilibrium between the c-cis and the c-trans isomers lies to the side of the c-trans[17,19,63,64]. The difference in free energy between the two isomers has been estimated[22] to lie between 2.5 and 3.1kcal mol^{-1}, with an energy barrier of about 3.9kcal mol^{-1}. From these results of electron diffraction[20,21] and the interpretation of IR and Raman spectra[18,23], in the ground state, trans-butadiene has the structure shown in fig.3.2. It is therefore planar,

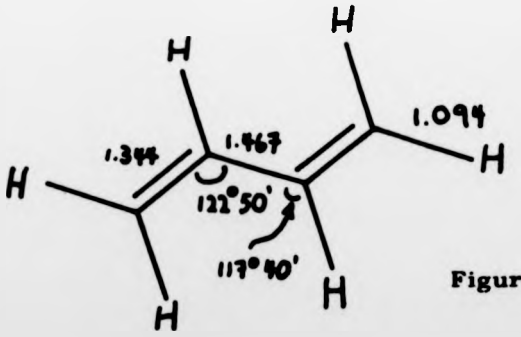


Figure 3.2

and the central C-C bond is longer than the terminal ones, although it is shorter than single bonds in saturated molecules (ca. 1.54 Å in

ethane). This shorter distance was explained by assuming that the central bond had some double bond character due to the delocalisation of π-electron density. The initial popularity of the Huckel Molecular Orbital (HMO) theory, with its disregard for σ-electrons[13], made this an attractive explanation. Taking benzene as a model in which π-electrons were completely delocalised (C-C bond length 1.397 Å), and ethane as a system with localised π-electrons, the length of the C-C bond in butadiene was intermediate. The contribution to bond-shortening by delocalisation was calculated[24-26] assuming that the covalent radii of carbon in C-C and C-H bonds were additive. These calculations indicated that the bond length was shortened by the change of hydridisation (sp^3 to sp^2) and electron delocalisation in roughly equal extents. This was promptly disputed by Dewar[27,28] who proposed that the bond lengths could be explained entirely by the effect of hybridisation differences, because the covalent radius of carbon in C-C bonds was affected differently by changes of hybridisation than in C-H bonds: the decrease in radius in going from sp^3 to sp^2 to sp was supposed to be greater for C-C bonds than for C-H bonds. This was supported by the fact that C-C bond lengths were constant among different compounds that presented the same sort of hybridisation. The bond length varied with the percentage of s-character of the bond; compounds like biphenyl, 4,4'-bipyridyl and butadiene[29,30] have very similar bond lengths.

Mulliken[31] stated that this view of the effect of hybridisation contradicted the results of quantum-mechanical calculations, which indicated some degree of delocalisation. Studies of Nuclear Quadrupole Resonance (NQR) indicate that delocalisation is important even

in alkanes[32], and explanation of ESR[33,34] and NMR[35] phenomena is made in terms of delocalised π-electrons.

Thermochemical measurements, either of heats of hydrogenation[36] or heats of formation[37], have been used to estimate the "resonance energy" of compounds with conjugated double bonds. Resonance energy is a measure of the difference in energy between the compound with conjugated double bonds and a model compound in which the anomalies of conjugated double bonds (e.g. bond shortening, effects of hydridisation, spatial interactions etc.) are not present. Pauling's approach[37] takes the bond energies corresponding to a theoretical model composed of fragments of non-conjugated molecules, assembles them, and sums bond energies to obtain a value that is compared to the experimental value for the heat of atomisation of the compound in question. The difference is the resonance energy. A similar approach has been proposed by Dewar[38-40] and Breslow[41], although in their case all the quantities concerned are theoretical. Not only is the model compound an idealisation, but the resonance energies are measured as the differences between two theoretical models. This approach has been praised for its clarity and unambiguity[43], but the results obtained do not relate clearly to any empirically measurable quantity.

On the other hand, the approach of measuring heats of hydrogenation involves the comparison of the heats of hydrogenating a conjugated compound and a model compound (e.g. benzene and cyclohexene), and a value of resonance energy could be obtained[36].

Severe criticisms have been leveled against both approaches, basically on two grounds:

a) that bond energies are not constant even in an homologous series, and

b) that resonance energy is not an internal property of a compound, directly measurable, but depends on the choice of model compounds.

In any case, there is greater thermochemical stability arising from double bond conjugation, although its exact measurement and significance is still disputed[8]. Thermochemical stability, however, is not a direct indicator of chemical reactivity. Allinger[44] has pointed out that although conjugation results in a lowering of the total energy of the molecule, the highest occupied molecular orbital (HOMO) is raised in energy, and the lowest unoccupied molecular orbital (LUMO) is lowered in energy, so conjugated molecules are more suceptible to nucleophilic, radical and electrophilic attack. We shall come back to this point in a discussion of the frontier orbital approach to reactivity, but first we must make two observations. The influence of conjugation is expressed in empirically obtainable parameters: thermochemical, NMR, IR, etc. Concepts such as resonance energy, delocalisation and hybridisation effects are products of the model employed for the description of the bonding situation[45]. The ultimate test for a bonding theory, of course, is its agreement with experiment. Calculations on the geometry of 1,3-butadiene using different models and approximations give different results[14-16,46], and it should be possible to decide for or against a bonding model by judging its performance against experiment. The problem is that all methods are approximate solutions of the Schrödinger equation, and refinements of the

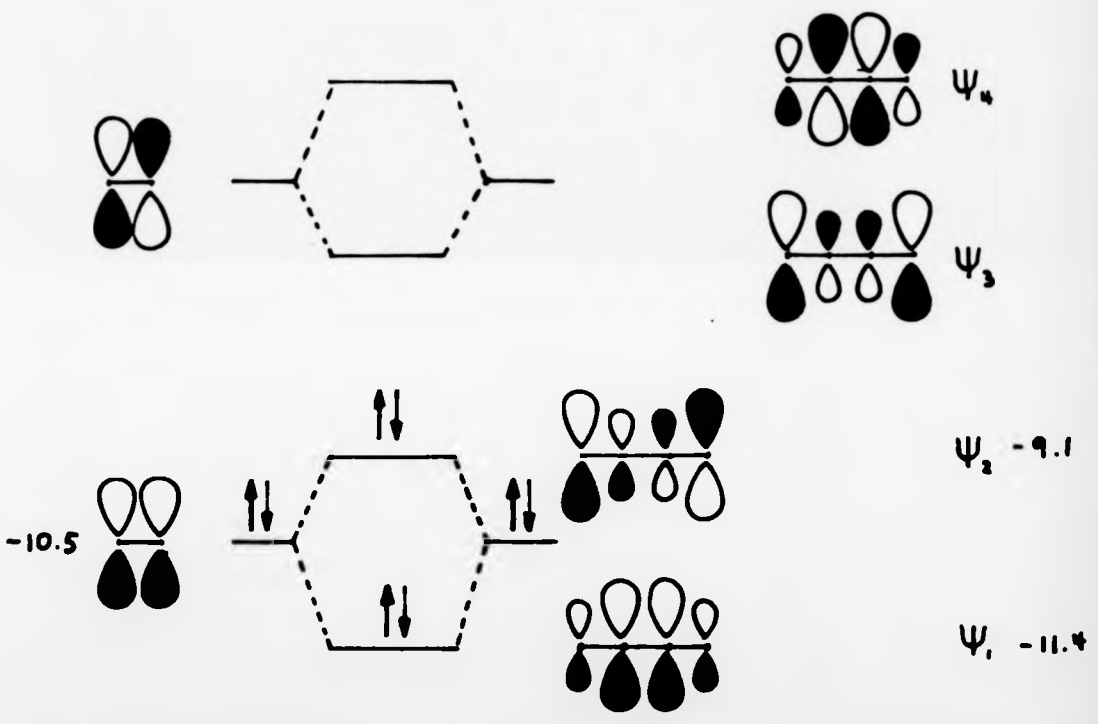


Figure 3.3 Molecular orbitals of Ethylene and 1,3-butadiene

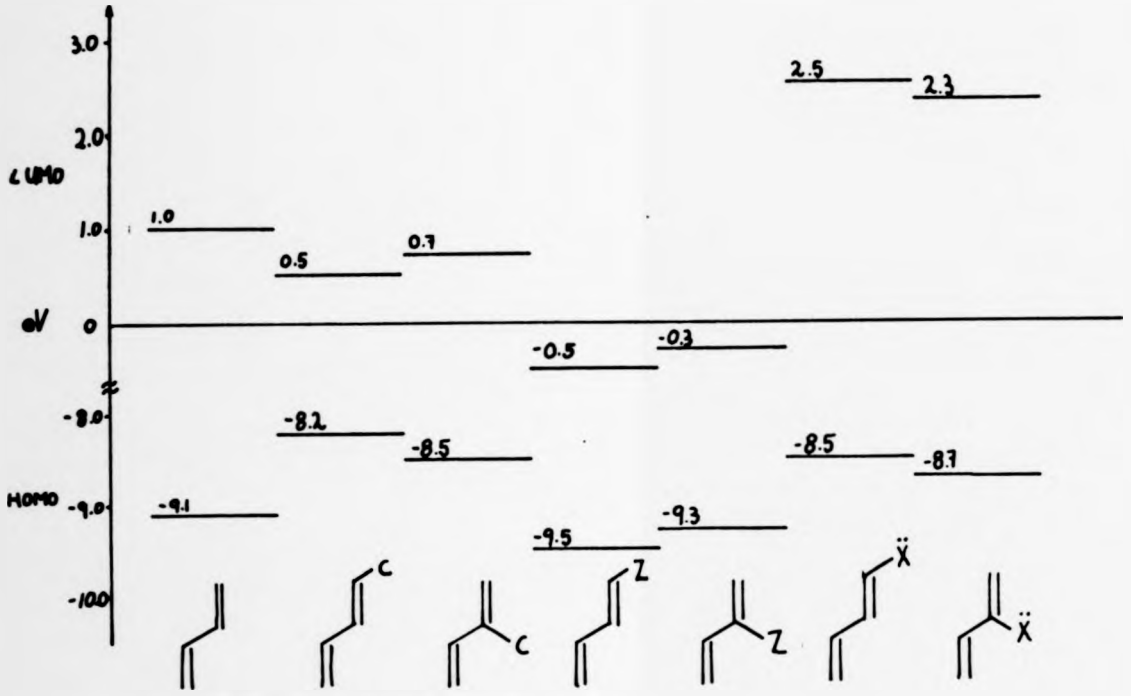
assumptions and approximations taken into account by a theory that has lost some popularity can bring it again to the fore of discussion. Such is the case of e.g. Valence-bond theory, which is experiencing a recent comeback, mainly through the work of Herndon[10-12], and others[47,57-60].

Intuitively, however, simple M.O. theory serves the purpose of providing an explanation and allowing predictions to be made, which, in spite of the great number of approximations involved, has a good record of agreeing qualitatively with experimental observations. Such is the case of Frontier Orbital theory, and we shall discuss the chemical effects of conjugation within that framework[48].

The Frontier Orbital Approach involves the building of molecular orbitals (LCAO), and the formation of Huckel-type (π-electron only) molecular orbitals. 1,3-Butadiene, therefore, is seen as a linear combination of two ethylene moieties, as illustrated in fig.3.3. The corresponding wave functions for the butadiene orbitals are:

$$\psi_4 = 0.371X_1 - 0.600X_2 + 0.600X_3 - 0.371X_4$$
$$\psi_3 = 0.600X_1 - 0.371X_2 - 0.371X_3 + 0.600X_4$$
$$\psi_2 = 0.600X_1 + 0.371X_2 - 0.371X_3 - 0.600X_4$$
$$\psi_1 = 0.371X_1 + 0.600X_2 + 0.600X_3 + 0.371X_4$$

where X_1, X_2, X_3 and X_4 are the corresponding Atomic orbitals. The energies of these orbitals have been estimated by photoelectron spectroscopy[49], and are shown in fig.3.4. The HOMO of ethylene is lower in energy than the HOMO of 1,3-butadiene by 1.4eV, and the LUMO of butadiene is lower than that of ethylene. Thermodynamic stability is derived from the π-electron energy, i.e. from



C = carbon moiety extending conjugation

Z = electron withdrawing group

X = electron donating group

Figure 3.4 Frontier Orbitals of 1,3-Dienes

the filled orbitals, but reactivity, on orbital terms, is controlled by the energies of the HOMO (for reactions with electrophiles) and the LUMO (for reactions with nucleophiles) of the reactant relative to the corresponding orbitals of the reagent. Thus, it is to be expected that 1,3-butadiene will react faster than ethylene both with electrophiles and nucleophiles, in strictly orbital-controlled reactions.

Adding electron-withdrawing groups at the 1- or 2- position of the diene results in a lowering in energy of both the LUMO and the HOMO; electron-donating groups will increase the energies of both frontier orbitals. Extending the conjugation, by adding another conjugated double bond, will increase the energy of the HOMO, and decrease the energy of the LUMO, as illustrated in fig.3.4.

Electrophilic attack on 1,3-dienes proceeds always at the terminus, because the intermediate generated is an allylic cation[61,62]. This allyl cation, however, may be captured by a nucleophile either at the other terminus, or at the 2- position, giving either formal 1,2- or 1,4- addition (see fig.3.5). The selectivity of

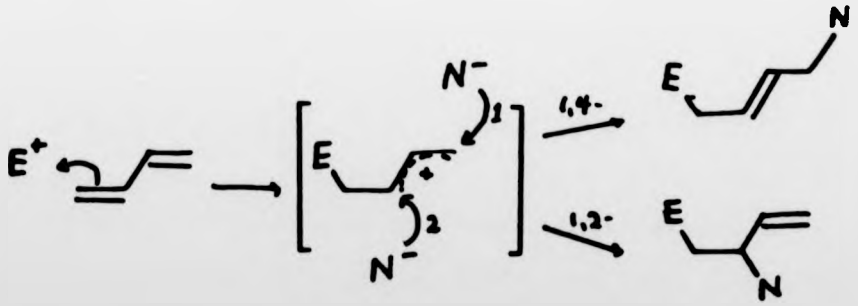


Figure 3.5 1,4 vs. 1,2-addition

this process is controlled by steric, solvation, ion-pairing[51], and stereoelectronic factors[50]. This will be discussed further in the following section, where some chemistry of conjugated dienes is illustrated.

Other effects of conjugation, like the exaltation of molecular refractivity[1,2] and the bathochromic shift and increased intensity of the UV/VIS absorption bands[52], have not been discussed here because they relate to the structure of the excited states of dienes, as well as to their ground states. The structure of the excited states of conjugated dienes[53-56] has been reviewed elsewhere, and is not directly relevant to our research, as all reactions studied by us seem to proceed through the ground state of the dienes.

3.3 Some Chemistry of 1,3-Dienes

We have shown that the synthetic problem posed by the transformation of β-turmerone into juvabione was to achieve oxidative functionalisation of the methylene terminus of β-turmerone. As mentioned above, our first choice[1] for achieving this transformation was a variant on hydroboration/oxidation procedures, as described by Brown[65] and Corey[66].

Hydroboration followed by cleavage of the resulting borane with alkaline hydrogen peroxide is an efficient method for achieving anti-Markownikow hydroxylation of unconjugated olefins[70,71]. The reaction is sensitive to steric constraints, and affords the corresponding alcohol with retention of configuration[70,73].

When 1,3-butadiene is treated with diborane, followed by alkaline hydrogen peroxide, a mixture of alcohols[74-77] is obtained. About 80% of the mixture is composed of butane-1,3-diol (24%) and butane-1,4-diol (76%). When conjugated dienes are present in excess over diborane, mono-hydroborated products may be isolated. Typical results are shown in the following table[71]:

Diene	Residual diene (after 1h)	Monohydroboration (%)
1,3-butadiene	50	4
isoprene	51	4
trans-piperylene	43	12
1,3-cyclohexadiene	24[a]	51[a]

When a substituted borane is employed for the hydroboration of 1,3-dienes, higher yields of mono-hydroboration products may be obtained. With diisoamylborane, at 0°C, 1,3-butadiene yields 8% mono-hydroborated product; with 1,3-cyclohexadiene mono-hydroboration is achieved in nearly 88%. On a preparative scale, however, using 100% excess of trans-piperylene, 74% yield of the terminal alcohol is obtained. The yields mentioned above are based on the borane used, not on diene present or converted, and therefore are not useful for preparative purposes. We reasoned, however, that a hindered borane would attack preferentially the methylene terminus of 10,11-dihydro-β-turmerone (12), and attempted the reaction with borane-dimethylsulphide complex[65], diisoamylborane[66], and 9-borabicyclo[3.3.1]nonane[71,78,80] (9-BBN). The

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a After 2h reaction

results were not conclusive, although complex mixtures appeared to be obtained from the reaction of boranes with compound (12). It was decided that a simple model compound was necessary to

(12) 10,11-dihydro-β-turmerone

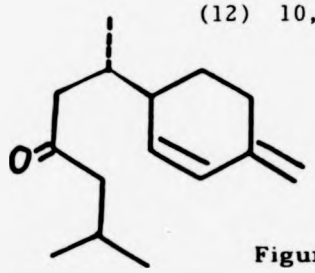

Figure 3.6

study the reaction. 4,4-Dimethyl-1-methylenecyclohex-2-ene (4) was synthesised according to the scheme in fig.3.7 (see also section 6.7), and subjected to hydroboration with 9-BBN. Still,

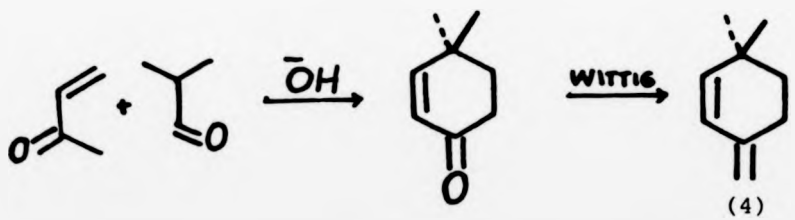

Figure 3.7

mixtures of alcohols were obtained. This is consistent with the observation that conjugated dienes react with boranes at a slower rate than isolated olefins. Thus, when a 1,3-diene reacts with a borane, the initial addition is slow, generating a mono-olefinic adduct which reacts rapidly with another borane molecule, generating the dihydroborated product. This occurs even with boranes as sterically demanding as 9-BBN or diisoamylborane.

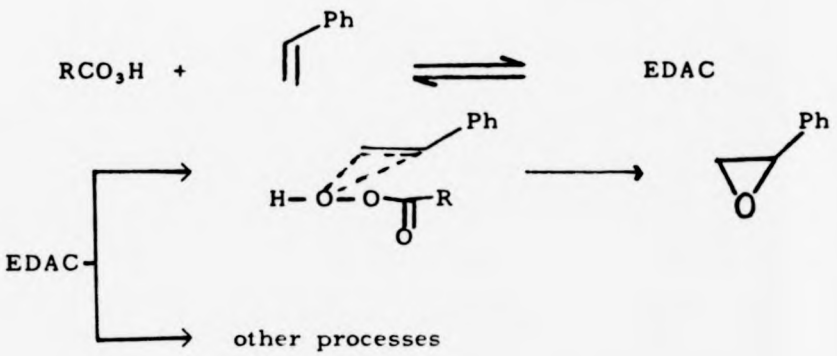

Figure 3.8 From Ref. 87

Epoxides have been prepared from olefins by the action of a variety of peracids[81-83,85], in what is known as the Prilezhaev reaction (especially in the Eastern Bloc countries). This is a selective method of oxidation of carbon-carbon double bonds in the presence of hydroxyl and carbonyl groups[83,86]. The mechanism of the epoxidation is believed to involve electrophilic attack on the olefin by the peracid[84,87]. This generates an electron donor-acceptor complex[87] (EDAC) which may rearrange to the epoxide and the acid (see fig.3.8) or may undergo other transformations. These other transformations involve the generation of ketones or aldehydes without the oxirane being an intermediate[87]. Under certain conditions[89-92], the product oxirane may also rearrange to carbonyl products, so the mechanistic landscape can be very complicated. The net result of the epoxidation is an oxygen transfer from the peracid to the olefin, and the rate of the reaction is enhanced by alkyl substitution on the olefin. Electron withdrawing groups on the peracid also increase the rate of oxygen transfer; thus, peracids increase in activity at a similar rate as their acidity increases[87].

Oxidation of β-phellandrene (15) by organic peracids has been reported[95]; the first double bond was oxidised in less than 1h with perbenzoic and perphthalic acids, and the second double bond was oxidised after 75h. The oxidation products identified were the monooxide and phellandral (16); the yield of phellandral increased when the oxidation was carried out at higher temperatures and in acidic media, which was consistent with the formation of a terminal mono-epoxide. Yields, however, were not quoted (see fig.3.9). These results prompted us to explore the possibility

of using this reaction to achieve the monofunctionalisation we required.

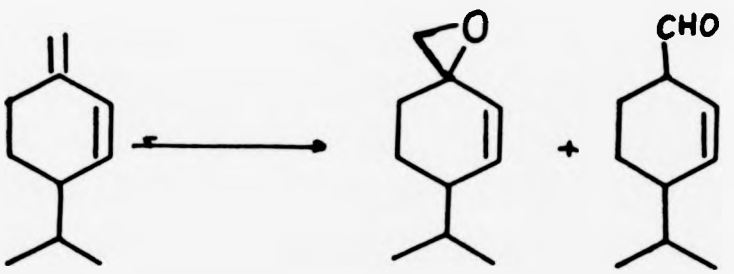

Figure 3.9 (16)

Using 4,4-dimethyl-1-methylenecyclohex-2-ene as a model compound, several peracids were studied. m-Chloroperbenzoic acid (MCPBA) in $CDCl_3$ resulted in isomerisation to the endocyclic diene, but this reaction was suppressed when the MCPBA was washed with pH7 aqueous buffer before use[102]. No epoxidation was evident after 10h at room temperature; higher temperatures caused decomposition of the peracid[96], but no epoxidation occurred. p-Nitroperbenzoic acid in dichloromethane did not react with the model compound; after ca. 10h at room temperature, the ^{1}HNMR spectrum of the reaction mixture was practically unchanged, even when excess peracid was employed, or the reaction was heated under reflux for 2h. When peracetic acid was used (40% peracetic acid in acetic acid), with the addition of solid sodium carbonate to neutralise any residual sulphuric acid, extensive epoxidation of the model compound occurred, but the reaction was not selective; complex mixtures were obtained, which could not be adequately characterised.

As mentioned above, electron-withdrawing moieties on the peracid accelerate the rate of oxygen transfer. Hydrogen peroxide is not sufficiently electrophilic to epoxidise an isolated carbon-carbon

double bond, but when the -OOH group is conjugated to a double-bond its reactivity is enhanced[101]. Payne[97,98] employed this by generating peroxyimidic acids by the base-catalysed addition of hydrogen peroxide to nitriles. These reagents are generally prepared *in situ*, and have found widespread application in the epoxidation of olefins[93,94,99,100]. Use of either acetonitrile or benzonitrile with hydrogen peroxide as the source of peroxyimidic acids, did not result in epoxidation of the model compound.

Epoxides which have been obtained with difficulty by direct epoxidation of the alkene, such as ethylene oxide, have been prepared with great ease from the alkene in a 2-step procedure *via* the alkene chlorohydrin[103]. Chlorohydrins can be prepared from olefins by the action of hypochlorous acid[104]. Hypochlorous acid can be formed *in situ* by chlorine in water[105], but is perhaps more conveniently prepared from yellow mercuric oxide and chlorine as a standardised solution in carbon tetrachloride[106].

When 1.4M hypochlorous acid was reacted with 4,4-dimethyl-methylenecyclohex-2-ene, and the crude product of this reaction treated with aqueous sodium hydroxide, the resulting yellow oil was a complex mixture, the products of which could not be identified. Presumably, chlorohydrin formation had not been selective. The mechanism of addition of halohydrins to olefins is electrophilic. The precise nature of the electrophile is still under dispute[107], because with aqueous hypochlorous acid the electrophile could be Cl_2O or H_2OCl^+; and both are more electrophilic than Cl^+. If there is initial attack on the olefin by the HOCl, generating a carbocation (see fig.3.10) in the case of 4,4-methylenecyclohex-2-ene, it was reasonable to expect that initial attack would occur

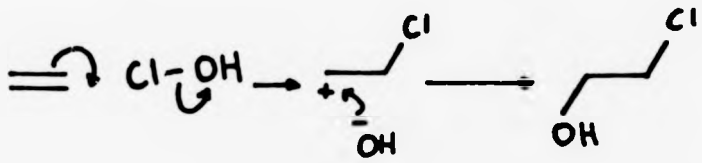

Figure 3.10 Addition of Hypochlorous Acid to Olefins

to generate the chlorohydrin at the methylene terminus. This supposition is made on steric grounds and the allylic stabilization of the intermediate carbocation. However, once more, the intermediate carbocation is short-lived, being rapidly captured by the nucleophile, generating a mono-olefin, which could react with more hypochlorous acid. Although we cannot be certain from our limited evidence, the complexity of the products obtained in our studies point to the possibility of competition between 1,2- and 1,4- addition, as well as further reaction of the mono-olefin generated after the initial addition.

This parallels the situation in the chlorination and bromination of 1,3-butadiene[108,109,112], where there is substantial competition between 1,2- and 1,4- addition, although proportions may vary with temperature, as in addition of HCl to dienes[110]. This points to kinetic vs. thermodynamic control, 1,2- addition being kinetically favoured. Nordlander[111] reported that 1,2- addition of DCl to trans-piperylene was kinetically favoured. This was difficult to explain if protonation (or deuteration) of the diene resulted in a symmetrical allylic cation: the chlorine could not differentiate between the termini of the cation on electronic grounds. The preference for 1,2- addition on kinetic control was explained by

the formation of ion-pairs which would equilibrate (see fig.3.11) before collapsing to products.

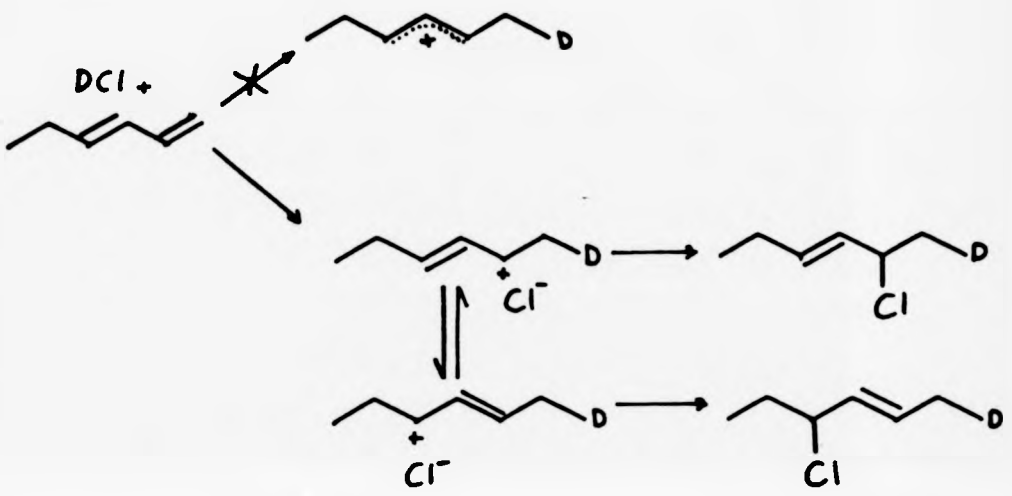

Figure 3.11 Ion-pairs in addition of DCl

It was clear, then, that successful mono-functionalisation of dienes would have to rely on a reaction that would give exclusively 1,2- or 1,4- addition, and that would be appreciably slower on the intermediate mono-olefin. The differentiation had to arise on either electronic or steric grounds, or both. It has been shown that severe steric constraints, such as those that arise during hydroboration with 9-BBN or diisoamylborane, are not sufficient. We had been over-optimistic in expecting a high kinetic preference for mono-epoxidation of the terminal methylene of 4,4-dimethyl-1-methylenecyclohex-2-ene.

Schwartz[113,114] reported the reaction between chlorobis(η^5-cyclopentadienyl)zirconium hydride and 1,3-butadiene[113] and <u>trans</u>-piperylene[114], to give terminally substituted, alkyl-zirconium compounds (see fig.3.12). He had previously reported[113] that similar

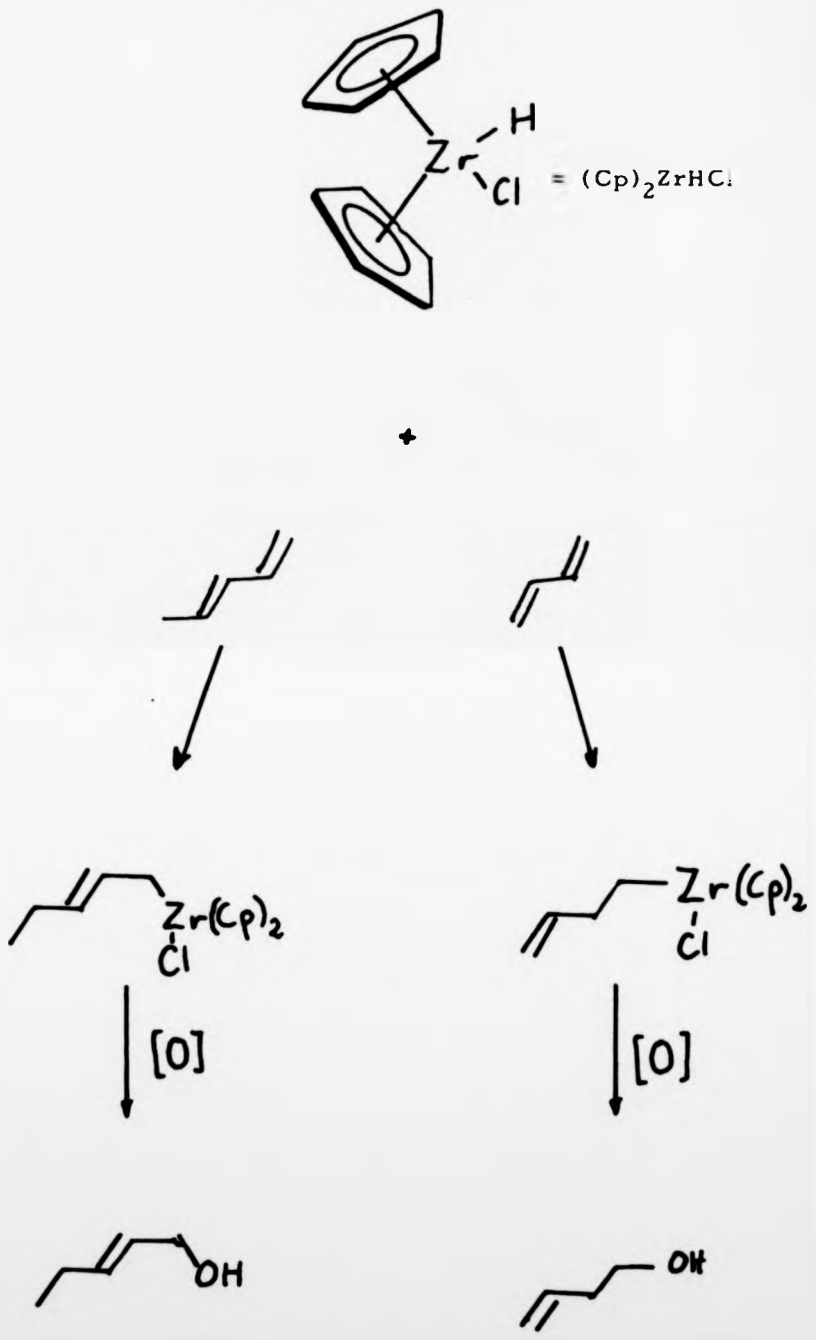

Figure 3.12 Hydrozirconation of 1,3-dienes

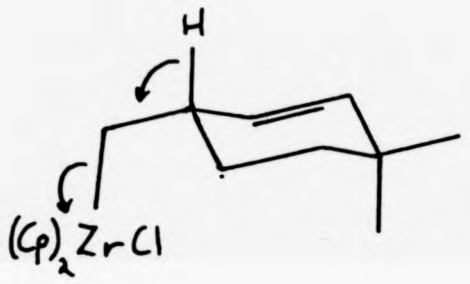

Figure 3.13 β-Elimination of Zirconium Adduct

alkylzirconium complexes could be oxidised to provide terminal alcohols. In this manner, hydrozirconation-oxidation would provide a route for terminal oxidative functionalisation of 1,3-dienes[115,116]. Chlorobis(η^5-cyclopentadienyl)hydridozirconium was prepared according to the procedure of Wailes[117,118] and reacted with 4,4-dimethyl-1-methylenecyclohex-2-ene in benzene for 4 hours. Dry oxygen was then bubbled through the solution, and after acid hydrolysis the only organic product isolated was unchanged starting material. None of the expected terminal alcohol could be detected. Presumably, if an alkylzirconium species is formed, the elimination depicted in fig.3.13 is facile. Other procedures for hydrozirconation are not suitable for conjugated dienes[119] or involve no substantial difference with the conditions attempted (e.g. ref.120).

We decided to continue our exploration of the reactions of 1,3-dienes with a metal hydride that was easily generated, and whose environment would place large steric demands on the 1,3-diene, to force metallation at the methylene terminus. The choice was a hydridocobaloxime, and the chemistry of this process is discussed in Chapter 5. Although this did not react with non-activated dienes, it constitutes an interesting side-road in our research, and its implications are still under investigation[121].

Many 1,2- and 1,4- additions to 1,3-dienes are known, although many do not seem to be selective. tert-Butylhypochlorite and hypobromite add to 1,3-dienes to give t-butyl ethers, although 1,2- and 1,4- addition has been reported[122,123]. Additions of nitroso compounds[124-126,128] result in 1,4-difunctionalised adducts, but the reactions are not really applicable to our synthetic problem.

Palladium-catalysed 1,4-acetoxychlorination of 1,3-dienes has been reported by Bäckvall[127], but the results are disappointing; 1,2- and 1,4- addition products, as well as regioisomers resulting from acetyl attack at either terminus of the unsaturated system, are produced. They are not preparatively useful reactions.

What was needed, therefore, was a 1,2- or 1,4- addition reaction which would

a) be selective for the less hindered terminus of the diene,

b) de-activate the resulting olefin to further addition.

This was satisfied by the addition of sulphenyl halides. As shown in the next chapter, sulphenyl halide addition to 1,3-dienes allows selective mono-functionalisation; something that none of the established methods of oxidative olefin functionalisation was successful in providing.

An alternative approach to the mono-functionalisation of 1,3-dienes could involve radical addition of a thiol to the unsaturated system[129]. The reactions with simple olefins are known to proceed to give the anti-Markownikow adduct. For example, the addition of thiophenol to styrene[130] gives the thioether in good yield (see fig.3.14). This thioether can than be chlorinated α- to

$$PhCH{=}CH \xrightarrow[AIBN]{PhSH} \underset{97\%}{PhCH_2CH_2SPh} \xrightarrow[\substack{2.\ Cu(II)\\ H_2O\\ acetone}]{1.\ NCS} \underset{60\%}{PhCH_2CHO}$$

Figure 3.14

the sulphur by N-chlorosuccinimide[136], and hydrolysis of the chlorothioether in the presence of Cu(II) to oxidise the thiophenol

produced, gives rise to the aldehyde. Such a procedure has been reported to give heptanal from 1-heptene, in 40% yield[131]. When a similar reaction was performed with a conjugated diene and 1-butanethiol, after 4 days irradiation only small yields of the desired product were obtained[132] (see fig.3.15). Reaction

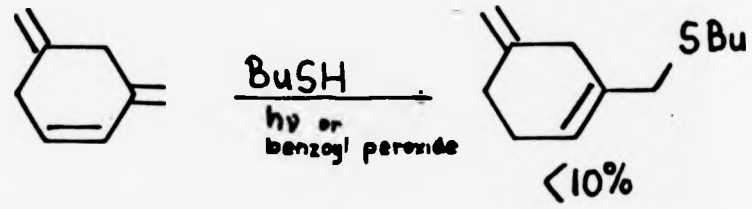

Figure 3.15

of 1,3-butadiene with thiophenol[133] gave mainly 1,4- addition. With cyclic conjugated dienes, however, mixtures of 1,2- and 1,4- adducts were obtained[134]. Addition of p-thiocresol to 3-methylenecyclohexene gave mainly the 1,4- addition product[135] (see fig. 3.16). The possibility of using this reaction to achieve the

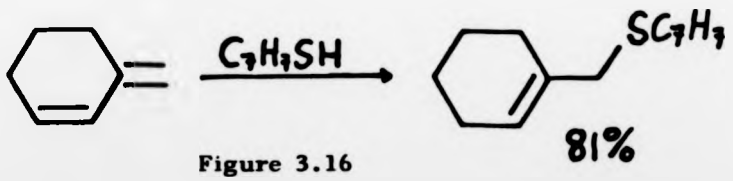

Figure 3.16

terminal functionalisation of methylene cyclohexene systems is very attractive. Although further work is necessary, a preliminary experiment in which thiophenol and 4,4-dimethyl-1-methylene cyclohex-2-ene were mixed with a small amount of 2,2-azo-bis(2-methylpropionitrile) (AIBN) provided no evidence of addition after 4h at room temperature. In view of the excellent progress made

with the addition of sulphenyl chlorides to conjugated dienes, this re-investigation could not be performed in the time available. It should not, however, be forgotten, as it seems that it could provide an alternative method of mono-functionalisation of 1,3-dienes.

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4 Sulphenyl Chlorides and Monofunctionalisation of 1,3-Dienes

4.1 General Remarks

The addition of sulphenyl halides to olefins forms part of the established armamentarium of organic chemistry. Pioneered by Kharasch[1,3], 2,4-dinitrophenylsulphenyl chloride became a standard reagent for the preparation of crystalline derivatives from olefins[2,4]. In the industrial production of mustard gas (1), a process not yet totally abandoned, sulphenyl chlorides are important

$$SCl_2 + C_2H_4 \longrightarrow ClCH_2CH_2SCl \xrightarrow{C_2H_4} ClCH_2CH_2SCH_2CH_2Cl \quad (1)$$

Fig.4.1 Mustard Gas Synthesis

intermediates. The methods of preparing sulphenyl chlorides[7,8], and much of their chemistry[5-11] has been reviewed. A large amount of work has been devoted to the study of the addition reactions of sulphenyl halides to olefins[12] since the first studies by Lecher and his co-workers[13] in 1925.

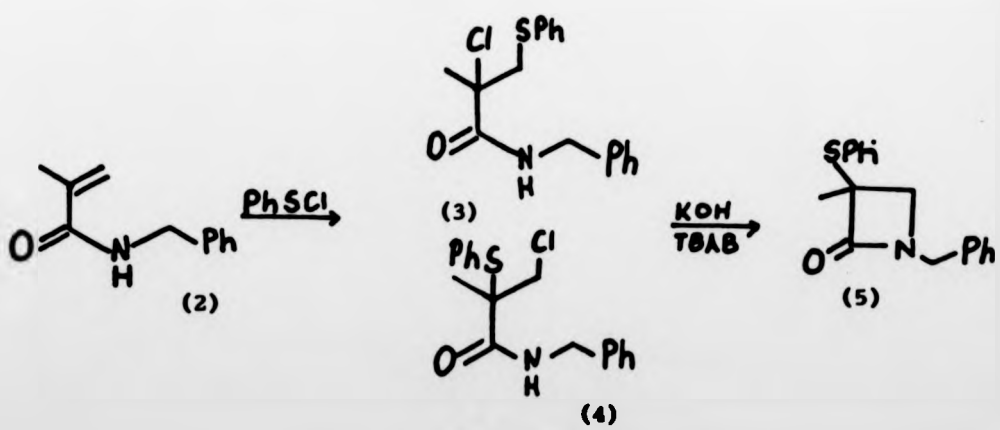


Figure 4.2 β-Lactam Synthesis

Addition of sulphenyl halides to olefins provides a very versatile functionalisation procedure. It has been used recently[14,15] for the construction of β-lactams from α,β-unsaturated amides as shown in fig.4.2.

The addition process can be followed by a dehydrochlorination, either as a separate step[16] or in a one-pot reaction[17], as illustrated in fig.4.3.

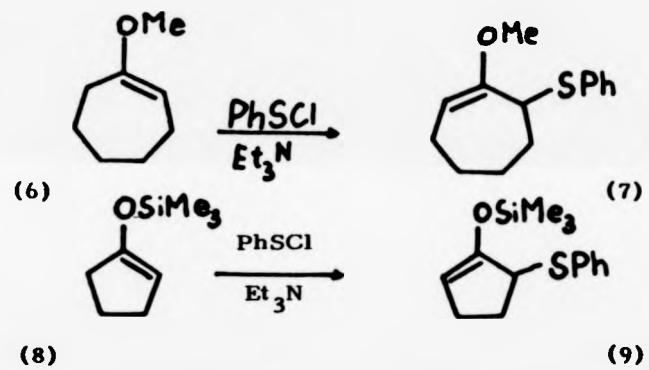


Figure 4.3 One-pot addition - dehydrochlorination

Addition of phenylsulphenyl chloride has also been used to generate allylic alcohols and ketones from moieties possessing a gem-dimethyl olefin (fig.4.4). This illustrates the ease with

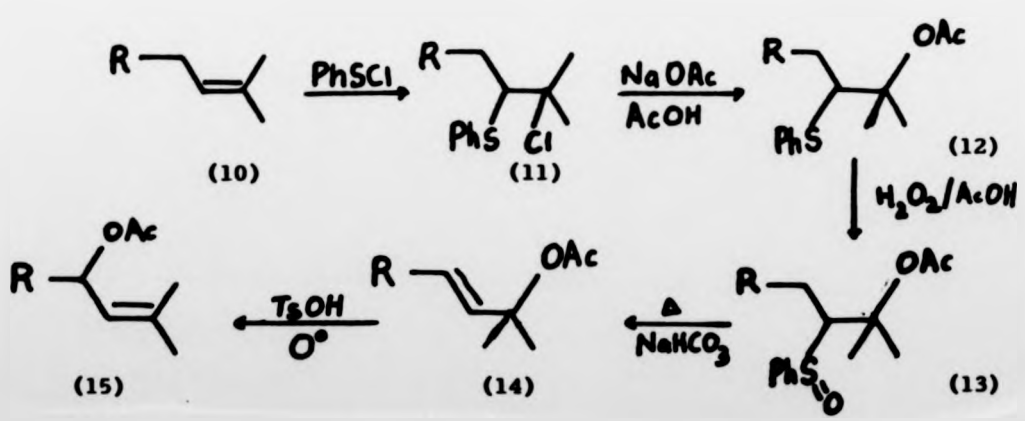


Figure 4.4

which the sulphide may be oxidised to the sulphoxide. This can be achieved with H_2O_2 in acetic acid[20] or a variety of other methods[18,19,21,22]. Thermal elimination of the sulphinic acid[24] proceeds in a similar way to the selenoxide elimination[23,25-29] away from oxygen to give olefins in high yield. Albeit, higher temperatures are necessary in the case of sulphoxides (80-100°C), than in selenoxides (0-20°C). In both cases, a β-hydrogen is necessary, and a 5-membered cyclic transition state has been postulated, as the stereochemistry of the elimination is syn[30,31].

Hydrogens α- to a sulphur group are much more acidic than those in hydrocarbons or those α- to oxygen. This has been explained as the effect of the empty d-orbitals on the sulphur, which overlap with the resultant carbanion and provide the additional stabilization[32]. Similar effects are observed with silicon[33,34], phosphorus[33] and chlorine[33]. The reality of this d-p π-overlap has been questioned[35] on the basis of MO calculations; ab initio SCF-MO calculations on $RSCH_2^-$, $ROCH_2^-$ and $RCH_2CH_2^-$ predict that stabilization of the carbanion, in the gas phase, is greatest for sulphur, followed by oxygen and least for CH_2, whether or not d-orbitals are included in the calculation. It has been suggested that polarisation of the electron distribution is a stabilising effect, and this is easier with the more polarisable sulphur than with O or C. The subject is still controversial, recent support for the d-p π-bonding[36,37] may not be enough to silence all the critics[38], but from a pragmatic point of view, it is relatively easy to form α-sulphenyl carbanions, and they can react with alkylating agents, aldehydes and ketones, add to multiple bonds and undergo many of the useful reactions of carbanions[33].

The sulphur moiety can be removed by reduction with Raney Nickel[39], or, as shown above, by oxidation and thermal elimination, to give olefins, or replaced by amines or ammonia[40].

In addition to the versatility achieved by functionalisation with sulphur compounds, it must be borne in mind that they are much less toxic and economical than the widely used selenium compounds.

The mechanism of the addition of sulphenyl chlorides to olefins has been thoroughly investigated, but some aspects are still the subject of controversy. The addition is almost invariably trans, as was observed by Cram[41]. The regiochemistry of the addition is generally that of Markownikow orientation[42], although anti-Markownikow addition products have been observed[43]. There are several peculiarities of this addition reaction: external nucleophiles are not usually incorporated even when the reaction takes place in acetonitrile or acetic acid; skeletal rearrangements are very rare, even with susceptible substrates like norbornene[47]; the reaction proceeds to give trans- adducts with cis- and trans-2-butenes from -40°C to 130°C, without loss of stereochemistry; and the addition to unsymmetrical olefins gives anti-Markownikow adducts. These observations led to the postulation of a strongly bonded, bridged episulphonium ion[44] as an intermediate, which was then attacked by chlorine at the least hindered side to give the corresponding adduct (fig.4.5). There are doubts, however, about the reality of this episulphonium ion as an intermediate in the addition of sulphenyl halides to olefins[46]. The mechanistic picture is more

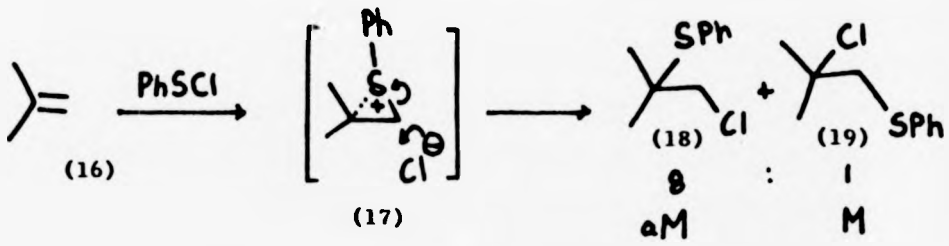


Figure 4.5 Addition of PhSCl to isobutylene[48]

complicated, even if some sort of 3-membered transition state must be involved, to explain the stereochemistry of the addition.

Although ionic dissociation of sulphenyl chlorides may occur in polar solvents[49], the supposition that the active electrophile is a dissociated sulphenium species, in dichloromethane, is not correct because practically no substituent effect is observed for 4-substituted phenylsulphenyl chlorides in the addition to E- and Z-1-phenylpropenes[50]. If the reaction is viewed as a nucleophilic substitution on sulphur, rather than an electrophilic addition, this points to an S_N2- type process, in which S-Cl bond breaking and C-S bond formation are roughly equal in the transition state. This may be contrasted with the behaviour of selenyl chlorides, where the rate studies of addition to the same substrates correlate with σ^+ to give ρ^+ values of -1.53(E) and -1.39(Z). This indicates that positive charge is developed in the transition state at both the selenium and the α-carbon, and therefore substantial Se-Cl bond breaking must occur in the transition state[50].

Returning to sulphenyl halide addition, then, after that first electronic attack the three-membered ring develops, but the chloride remains closely associated to the sulphur, by forming an intimate

ion pair (see fig.4.6). Dissociation continues, to form a solvent-separated ion-pair. The rate determining step, however, is the initial electrophilic attack[51], and further rearrangement of the ion-pairs does not affect the rate of the reaction. However, product composition may be affected by the addition of salts which may displace the chlorine from the solvent-separated ion-pair[51,52]. This ion-pair then rearranges, but how this occurs is not clear. Intermolecular attack seems unlikely, as solvent participation (i.e. with CH_3CN or CH_3COOH) is not observed, so it is proposed that the ion-pairs rearrange to give a suitably placed chlorine for trans-substitution, which collapses to products. In fig.4.6, this process is shown: (1) and (5) are intimate ion-pairs, (2) and (4) are solvent-separated ion-pairs, and (3) is a dissociated, fully solvated species.

In summary, then, from a pragmatic viewpoint, the stereochemistry of addition is trans, and the chlorine attacks the more positively polarised C-atom of the intermediate giving mainly anti-Markownikow products: the reaction is governed by charge control, and steric effects are not dominant except with tert-butyl substitution of the olefin, although they are already important in isopropyl-substituted olefins[53].

Reactions of phenylsulphenyl halides with conjugated 1,3-dienes were reported to give products of 1,4- addition, but these were shown to be the result of a rearrangement of the kinetically preferred 1,2- adducts[54,55]. With one equivalent of sulphenyl halide mono-adducts were formed, and no di-adducts were detected. Either the reaction with non-conjugated olefins is slower than

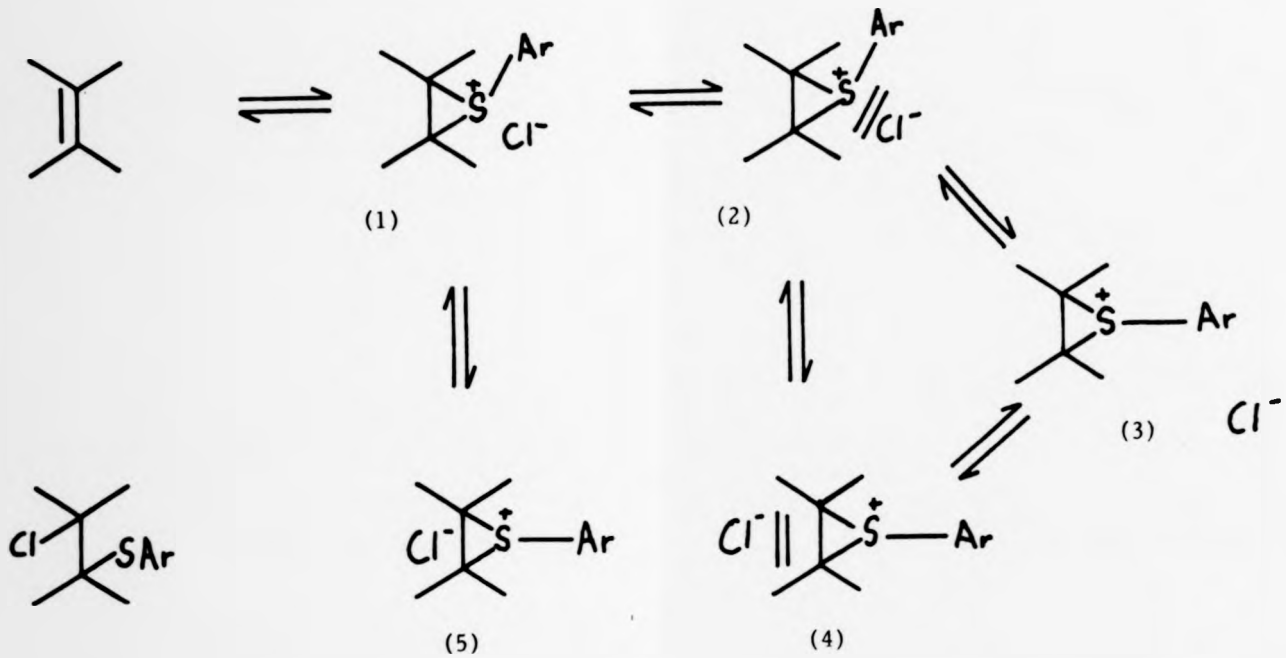


Figure 4.6 Ion-pairs in the addition of ArSCl to olefins: (1) and (5) are intimate ion-pairs, (2) and (4) are solvent-separated ion-pairs, and (3) is a dissociated, fully solvated species.

with conjugated dienes, or the positively charged intermediate is long-lived enough to protect the diene from a second attack, so all the reagent is used up before the intermediate collapses. The rate of addition of methylsulphenyl chloride to 1-butene is substantially faster than that to 1,3-butadiene, as a competition experiment gives a 7:3 ratio of products, in favour of the butene adduct[55]. The 1,2-adducts can isomerise more or less readily, according to solvent polarity, temperature and nature of the sulphide. Methylsulphenyl chloride adducts rearrange more readily than the corresponding phenylsulphenyl adducts[55], presumably because the electron density at sulphur, and therefore the nucleophilicity, is lessened by conjugation. In our work, it was necessary to heat the 1,2- adduct from 2,3-dimethylbutadiene and phenylsulphenyl chloride at 40°C for 72h to effect complete rearrangement. Mueller and Butler[55] studied the rearrangement of methylsulphenyl chloride adducts of piperylene , 4-methyl-1,3-pentadiene , and isoprene

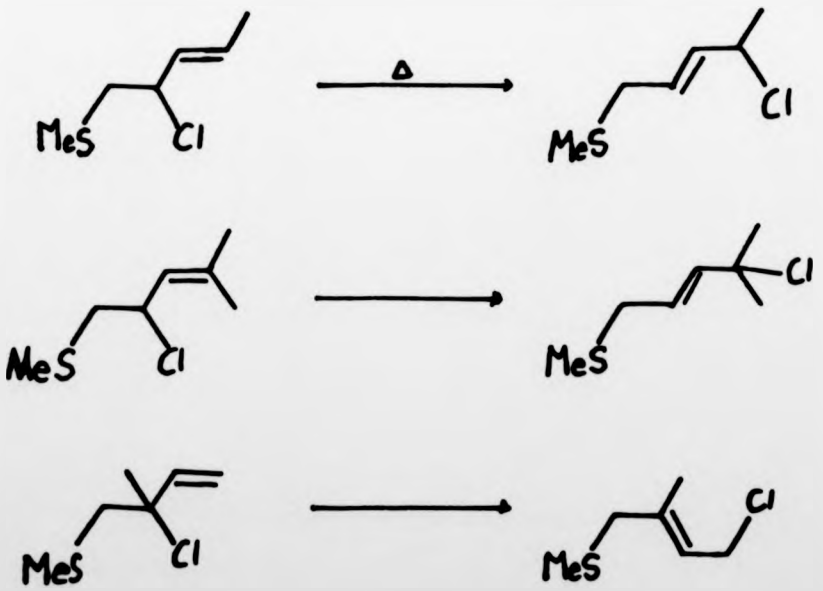


Figure 4.7 Rearrangement of 1,2-adducts

(see fig.4.7) and found that the adduct from piperylene was the most readily rearranged, with equilibrium being reached after about 70h at room temperature. The other two adducts were slower in rearranging by a factor of 5-10; acid catalysis, however, greatly accelerated the isomerisation. The selectivity of the reaction merits comment: in isoprene, attack of both methylsulphenyl chloride and phenylsulphenyl chloride showed a slight preference for the more substituted double bond (57:43) but for piperylene the selectivity was for the terminal double bond (86:14).

In a study of the rates and products of addition of 4-chlorophenylsulphenyl chloride to several 1,3-dienes, Schmid and his co-workers[56] found that substitution of a hydrogen of 1,3-butadiene by a methyl group increased the rate of addition. They also found that a preference for addition at the least substituted double bond, and the stereochemistry was strictly anti-. They found that the initial mixtures contained 5-10% 1,4- adducts, but that is not surprising, as the additions were preformed at 25°C.

The isomerisation can be readily understood if the initial addition is reversible. As shown in fig.4.6, the covalent 1,2- adduct can re-ionise to give an intimate ion-pair and a solvent-separated ion-pair. Fig.4.8 shows the isomerisation pathway; the ion-pair

Figure 4.8

can rearrange through a higher energy transition state to an ion-pair of the 1,4- adduct, which then collapses irreversibly to the covalently bonded 1,4- adduct.

Among isolated examples of addition of sulphenyl halides to 1,3-dienes, two cases merit mention. First, the synthetically useful addition of phenylsulphenyl chloride to O-silylated dienolates[57] to give γ-sulphenylated α,β-unsaturated aldehydes, achieving sulphenylation and deprotection of the silyl enol ether in one pot (fig.4.9):

$$CH_2{=}CHCH{=}CH_2OSiMe_3 \xrightarrow[88\%]{PhSCl} PhSCH_2CH{=}CHCHO$$

Figure 4.9

The second is the preparation of dienyl thioethers by sulphenylation/dehydrochlorination of 1,3-butadiene[16], and diene carbamates[58], which are useful for Diels-Alder reactions (see also ref.59).

Before proceeding to discuss our work in this area, it must be said that there are other, excellent methods of sulphenylating olefins[63,64] especially those developed by Trost[60,61,65].

However, there is little precedent for their reactions with 1,3-dienes.

4.2 Results and Discussion

We have already illustrated the versatility that arises from sulphur-substitution of organic compounds. The addition of sulphenyl

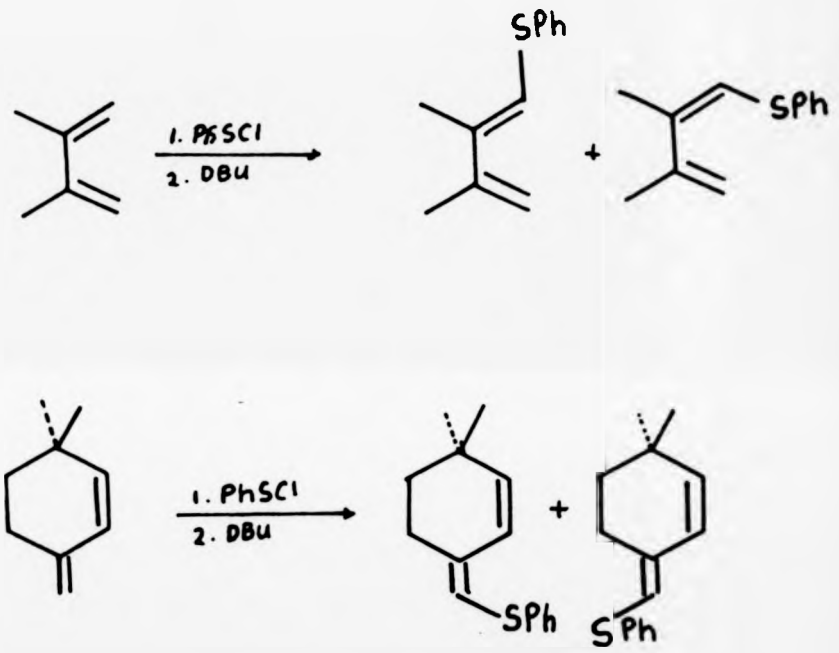


Figure 4.10 Sulphenyl halide addition followed by dehydrohalogenation

halides to 1,3-dienes proceeds to give the kinetically favoured 1,2- adduct, with the sulphide moiety at the least hindered terminus of the initial diene. Following thermal or acid catalysed rearrangement, which is almost quantitative, the 4-position is readily functionalised. Thus, the mono-functionalisation of 1,3-dienes involves an initial di-functionalisation. The additions are selective; so are the rearrangements. The problem that remained was how to convert either the 1,2- or the 1,4- difunctionalised product into a terminally mono-oxidised product.

In this context, it was known that vinyl sulphides had been hydrolysed to aldehydes and ketones by a variety of methods, from simple acid treatment[66,67,72,73,78], mercury (II)-catalysed hydrolyses[68-71,74], and $TiCl_4$-catalysed hydrolyses[75]. These methods, however, are not generally applicable, and some substrates prove very difficult to hydrolyse in good yield[74]. Other methods of generating aldehydes from vinyl sulphides involve addition of thiophenol or HCl, to generate the α-substituted sulphides which could be more readily hydrolysed either as the thioketals[76-78] or the α-chlorosulphides[74].

Addition of phenylsulphenyl chloride to either 4,4-dimethyl-1-methylenecyclohex-2-ene or to 2,3-dimethylbuta-1,3-diene proceeded to give a 1,2- adduct in good yield (see sections 6.7.5 and 6.3.1); these were dehydrohalogenated by the procedure of Hopkins and Fuchs[16], to give the corresponding dienyl sulphides.

Attempts at acid-catalysed or Hg(II)-catalysed hydrolysis did not produce any carbonyl compounds, but complex mixtures of

organic products, which were not characterised. Acid-catalysed addition of thiophenol or HCl, did not produce the desired α-substituted sulphides, and although the possibilities were not exhaustively explored, it was decided to attempt a different approach.

Sulphoxides were found to react with acetic anhydride by Pummerer[79] to give α-acetoxy sulphides, which hydrolysed readily

Figure 4.11

to give aldehydes. This reaction has been used extensively for the synthesis of aldehydes from sulphoxides[80-82], and when chiral sulphoxides are used, transfer of chirality to the α-carbon gives chiral α-acetoxysulphides with modest enantiomeric excess (10-70%)[83].

The mechanism of the rearrangement[84,85] involves initial sulphoxide O-acylation and breakdown of this species by the sequential loss of a proton and dissociation to an intimate ion-pair. This ion-pair rearranges to the product-determining ion-pair, and collapses to give the α-acetoxy sulphide (see fig.4.12). A recent procedure[86] uses trifluoroacetic anhydride instead of acetic anhydride, which results in fast Pummerer rearrangement and easily hydrolysed products.

The 1,2- adduct of phenylsulphenyl chloride and 2,3-dimethylbutadiene rearranged readily to the 1,4- adduct on heating in acetonitrile at 40°C, in about 70h. Heating at higher temperatures

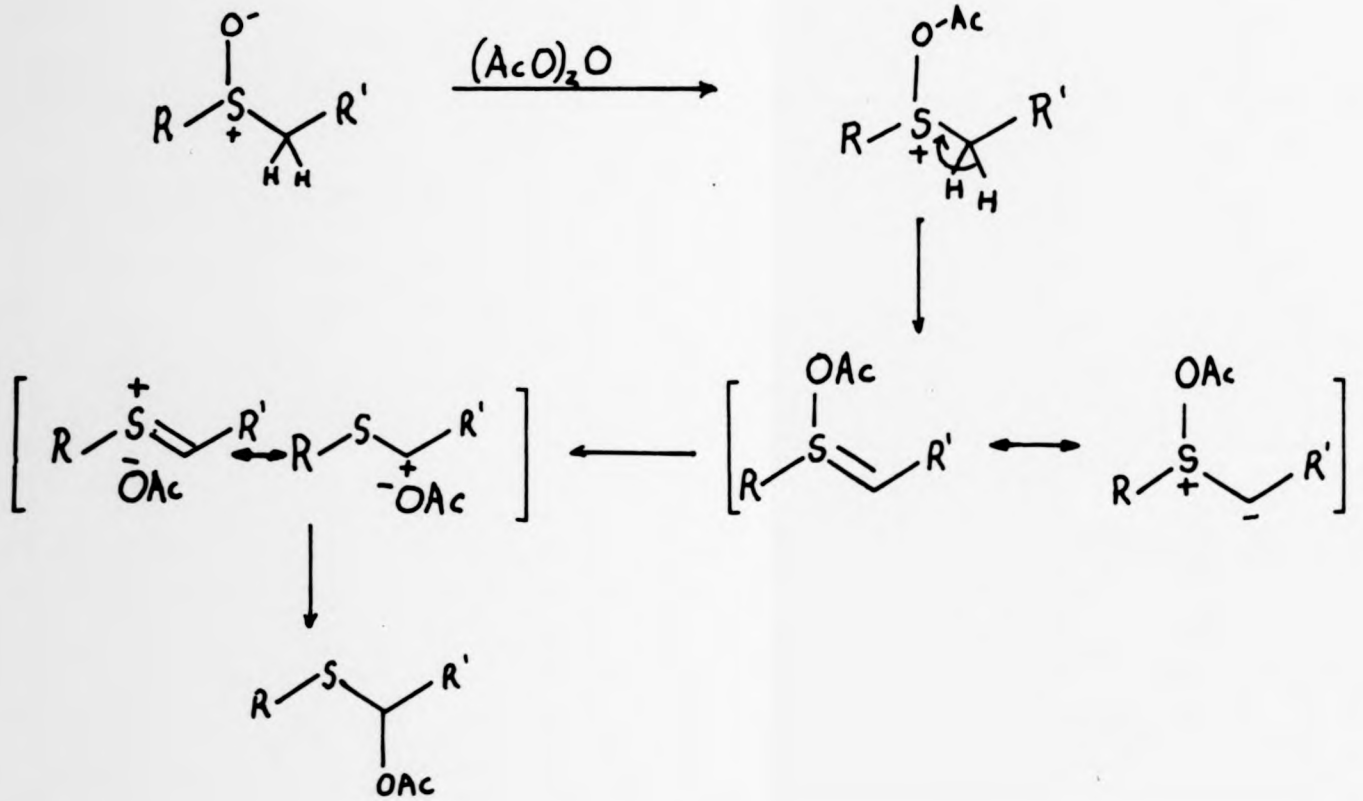


Figure 4.12 Pummerer Rearrangement

results in concomitant dehydrochlorination, and lower yields of the 1,4- adduct. This chlorosulphide could be easily dechlorinated by reaction with lithium triethylborohydride in THF (see below) to give the unsaturated sulphide, which was then oxidised to

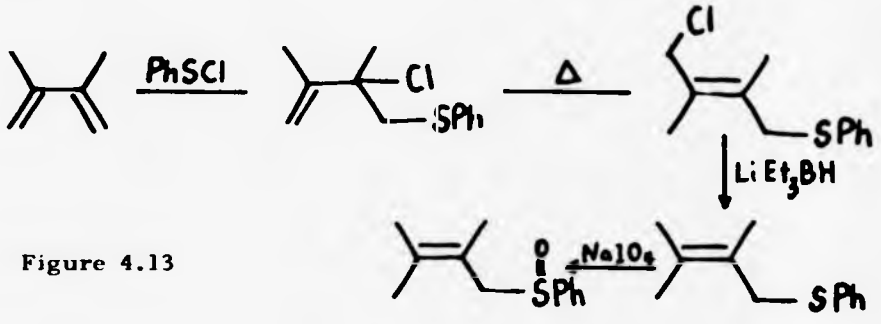


Figure 4.13

the sulphoxide by sodium periodate in aqueous ethanol. When this sulphoxide was treated with trifluoroacetic anhydride, however, no α-trifluoroacetylsulphide was formed, and attempted hydrolysis of the mixture gave no aldehyde (^{1}HNMR). A peak appeared at 6.2 ppm, indicating that the dienyl sulphide had been formed. This was explained by postulating loss of a proton in the intermediate

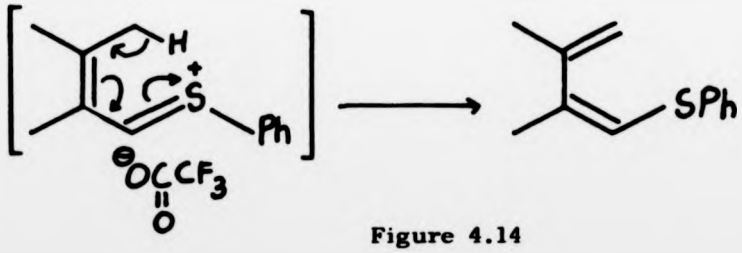


Figure 4.14

(1) being faster than collapse of the ion-pair to the α-substituted sulphide. By preparative TLC, a sample of this dienylsulphide was isolated, and shown to be identical to that prepared by dehydrochlorination of the 1,2- adduct of 2,3-dimethyl-1,3-butadiene and phenylsulphenyl chloride. This constituted 50% of the

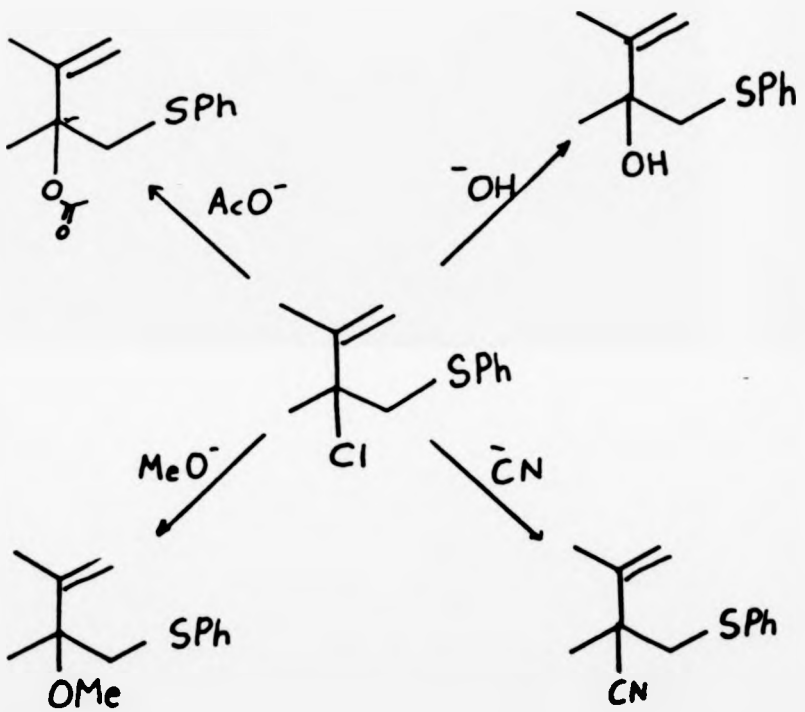


Figure 4.15

reaction mixture, and the remaining products were not identified. It was thought that perhaps, a more nucleophilic acetate group might generate the desired α-substituted sulphide intermediate. However, because no aldehyde products had been detected in the trial reactions, an alternative approach had to be found.

It had been shown previously that the chlorine in β-chlorosulphides could be replaced, with retention of configuration at carbon, by a variety of nucleophiles[45], and this was taken to be indicative of anchimeric assistance in the solvolysis process, involving a sulphur-bonded intermediate. It is not clear what the structure of the intermediate is (cf. discussion above, concerning the mechanism of the addition of sulphenyl halides to alkenes), but the astounding rate acceleration and retention of stereochemistry imply that some episulphonium-like intermediate is involved. By the principle of microscopic reversibility, it ought to be identical to the intermediate in the addition of sulphenyl chlorides to double bonds[87-90].

Oxygen nucleophiles, such as MeO^- and ^-OH, gave the 1,2-difunctionalised products in good yield (see fig.4.15). Attempts to trap the intermediate with sodium borohydride in DMF gave mixtures of reduced products. This implies that there is competition between attack at C-4 and C-2 of the intermediate. When reduction takes place at 80°C, rearrangement competes with the attack of hydride at the tertiary centre. Although the product of rearrangement, the 1,4- adduct could generate the same eposulphonium species as the 1,2- adduct, it may alternatively suffer reduction by an S_N2 process. It was necessary to heat the reaction mixture for 3h at 80°C to obtain high yields of the reduced products

(~ 60% combined yield). Lower temperatures or shorter reaction times gave incomplete reduction of the tertiary chloride.

The reduction of this tertiary chloride with tetra-n-butylammoniumborohydride in CD_3CN at 75°C was followed by ^{1}HNMR (see section 6.3.5), and similar results were obtained: a 2:1.5 mixture of 2,3-dimethyl-1-(phenylthio)but-2-ene and 2,3-dimethyl-1-(phenylthio)but-3-ene. Attempts at reducing the tertiary chloride

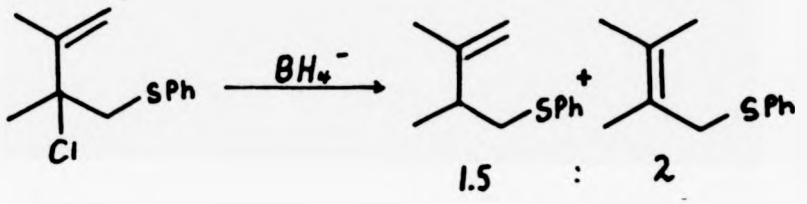


Figure 4.16

with lithium triethylborohydride in THF at room temperature were not successful: no reaction had occurred after four days. The rearranged product, (14) however, could be readily reduced (see section 6.3.7) to give 2,3-dimethyl-1-(phenylthio)but-2-ene:

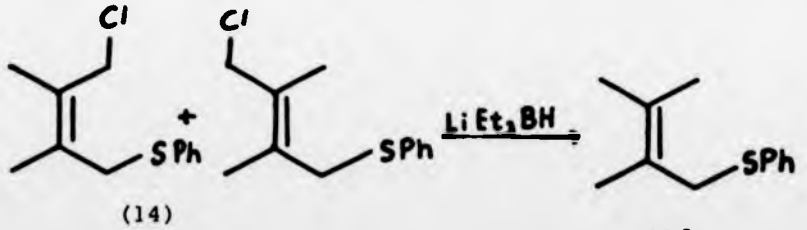
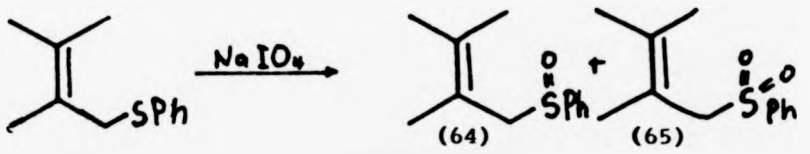


Figure 4.17

in 3h at 25°C. It was this product which was oxidised with methanolic sodium periodate to the corresponding sulphoxide. Surprisingly, oxidation with excess of sodium metaperiodate for 20h at room temperature resulted in a 2:3 mixture of the corresponding

sulphoxide and sulphone:



(62) Figure 4.18

It became clear that replacement of the chlorine of the β-chlorosulphide by a nucleophile gave the 1,2- adduct; if this could not rearrange. In the case of trapping by hydride ion, the reaction was slow, and rearrangement of the starting material generated a more reactive species, the primary chloride or its

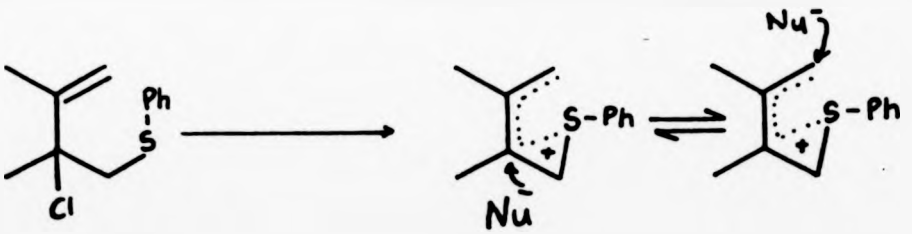
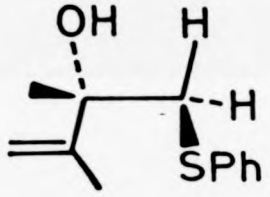


Figure 4.19

precursor ion-pair.

Replacement of the chloride with 1M NaCN in H_2O-CH_3CN gave 14% of the required nitrile. A saturated solution gave 55% of the same compound. In both cases the corresponding hydroxide was a contaminant, but could readily be removed by chromatography. Presumably, the use of a dipolar aprotic solvent or of a substituted alkyl-ammonium cyanide would increase the yield of these potentially useful species.

Using aqueous sodium hydroxide in dioxan or acetonitrile

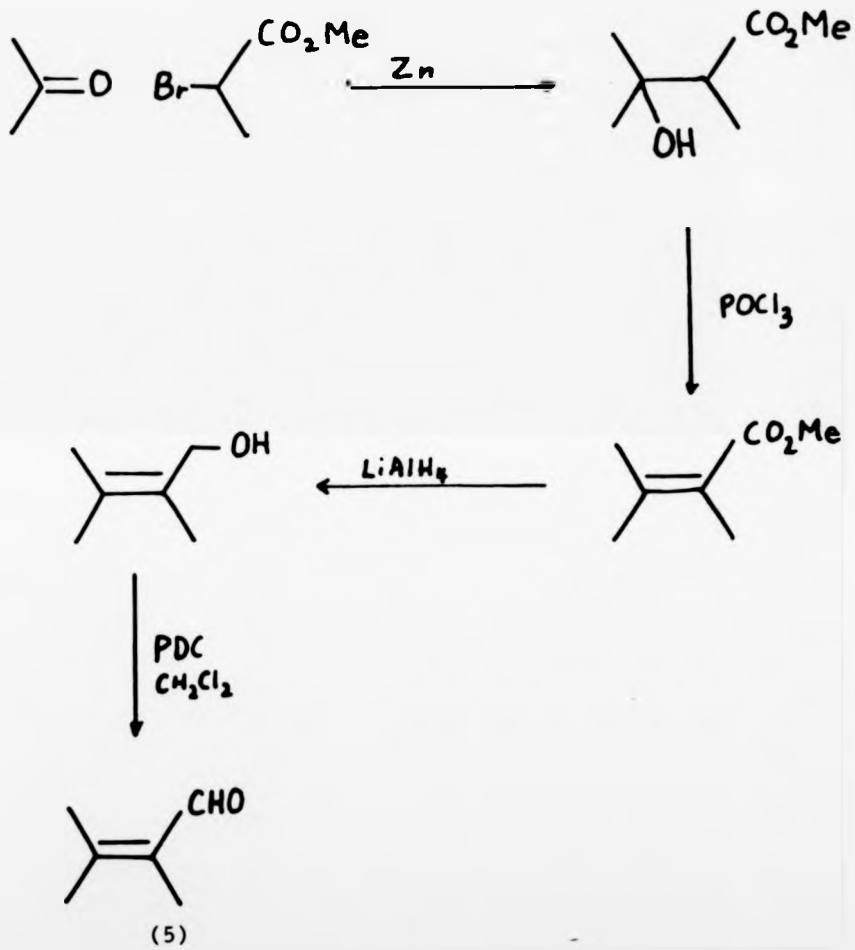


(11)

for the obtention of the β-hydroxysulphide from the chloride was not a satisfactory procedure; crude yields were of the order of 60%, and the product was impure. Chromatography of these β-hydroxysulphides often resulted in decomposition. Silica gel, with or without triethylamine in the eluant, was not satisfactory, but on a small scale, neutral alumina was successfully employed for the purification. This purification step was obviated by the use of the silver-assisted hydrolysis procedure (see section 6.3.14). The crude product from this reaction was essentially pure β-hydroxysulphide.

Pirkle and Rinaldi[91,92] have previously converted β-hydroxysulphides to oxiranes by the methylation of the sulphide with trimethyloxonium fluoroborate followed by base treatment. Initial attempts at repeating their procedure on β-hydroxysulphide (11) were not immediately rewarding; the oxirane, if formed, was very delicate and could not be isolated readily.

To obtain further information about the applicability of this protocol, a mixture of β-hydroxysulphides was prepared by the action of sodium thiophenoxide on styrene oxide. This 3:2 mixture of regioisomers (section 6.6) was treated with trimethyloxonium fluoroborate in dichloromethane, and the resulting salts reacted with sodium hydride. A 1:1 mixture of methylphenylsulphide and styrene oxide was obtained in 98% yield. Analytical samples of both compounds were obtained by preparative TLC. This indicated that the protocol was not at fault, so it was decided to generate the oxirane from 2,3-dimethyl-1-(phenylthio)but-3-en-1-ol using this procedure, but to rearrange this epoxide to an aldehyde by treatment with acid, and to characterise this aldehyde.



(5)

Figure 4.20

An authentic sample of the aldehyde was prepared, as shown in fig.4.18. Reformatsky reaction of methyl 2-bromopropanoate and acetone gave the alcohol (2). Dehydration of this alcohol was surprisingly difficult; mild dehydration procedures had no effect, but phosphorus oxychloride finally gave good results, and the α,β-unsaturated ester was obtained.

Corey[93] has claimed that diisobutylaluminium hydride (DIBAL) can reduce methyl esters to aldehydes. With one equivalent of DIBAL in CH_2Cl_2 at -78, no aldehyde could be seen, only starting material was recovered after work-up. Two equivalents of DIBAL, under the same conditions, generated the alcohol. This alcohol could be obtained more readily by reduction with lithium aluminium hydride, without conjugate reduction of the double bond. Oxidation of the alcohol to the α,β-unsaturated aldehyde proceeded readily with pyridinium dichromate in CH_2Cl_2.

With the α,β-unsaturated aldehyde at our disposal, we decided to attempt to synthesize it from the β-hydroxysulphide in a 1-pot reaction, without isolation of the intermediate epoxide. It was expected that conjugation of the double bond with the aldehyde would occur under the acid-catalysed conditions. This proved to be so, and the aldehyde isolated (as its DNP) from the reaction mixture was identical to that prepared by the alternative route (see section 6.3.15). Recovery of the aldehyde as its DNP, from the reaction mixture, was not consistent; yields varied between 12-46%. It was clear from the ^{1}HNMR of the reaction mixture, that the aldehyde was present in a higher proportion than the recovery of DNP would lead us to believe. Perhaps

the strongly acidic conditions were to blame; but the preparation of the dinitrophenylhydrazone of the aldehyde obtained from the sulphur-free protocol proceeded in good yield.

At any rate, the monofunctionalisation had been achieved; it remained to attempt it on other 1,3-dienes. Addition of phenylsulphenyl chloride to 4,4-dimethyl-1-methylenecyclohex-2-ene, followed by silver-catalysed hydrolysis, gave the corresponding β-hydroxysulphide in 68% yield. This was then subjected to the reaction with trimethyloxoniumfluoroborate, and base treatment. Once more, the oxirane proved to be troublesome to handle, and it was synthesised by an alternative procedure, as shown in fig.4.21. 4,4-Dimethylcyclohex-2-en-1-one was synthesised by Robinson annelation of methylvinylketone and isobutyraldehyde (see section 6.7.1). Formation of

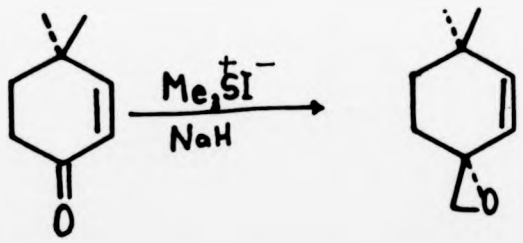


Figure 4.21

the epoxide with dimethylsulphonium methylide is assumed to proceed by a similar pathway to the procedure we want to utilise to

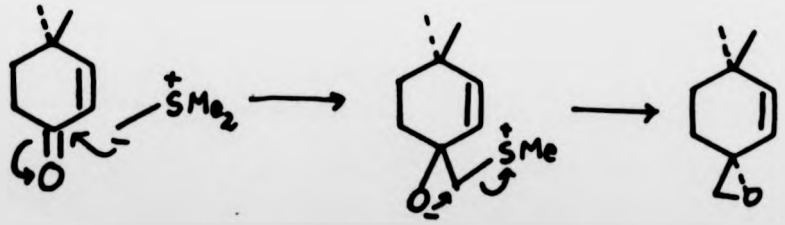


Figure 4.22

obtain epoxides from β-hydroxysulphides. Attack of the methylide on the ketone generates an alkoxide which displaces a sulphonium species, thus giving rise to the epoxide. This reaction proceeded without problems, but some starting ketone remained. This mixture, however, was treated with p-toluenesulphonic acid, and the resultant product treated with 2,4-dinitrophenylhydrazine. The hydrazones were separated and used as authentic standards.

The yields of aldehyde from the β-hydroxysulphide arising from 4,4-methylenecyclohex-2-ene were variable. It was thought that contamination with diphenyl disulphate, arising from reaction of phenylsulphenyl chloride and thiophenol during the preparation of the reagent, was responsible for the variability. As the formation of epoxide from the ketone with the methylide proceeded so well, it was decided to use methylsulphenyl chloride, prepared from sulphuryl chloride and dimethyldisulphide. This was distilled before use, so disulphide contamination could be avoided; such contamination could be detected by ^{1}HNMR.

Addition of methylsulphenyl chloride to 1,3-dienes proceeds in the same way as phenylsulphenyl chloride, but the adducts rearrange more readily. This can be avoided by immediate silver-assisted hydrolysis of the chlorosulphide. Methylation of the sulphur, followed by treatment with sodium hydride, generated the epoxide. This epoxide was rearranged to the conjugated aldehyde by treatment with acid.

The only step that remained was the oxidation of the unsaturated aldehyde to the α,β-unsaturated methyl ester. This was performed

on 4,4-dimethyl-1-formylcyclohex-1-ene using the procedure described by Corey[95,96]. This consists in MnO_2 oxidation in the presence of cyanide and methanol. Cyanide attacks the aldehyde, forming the cyanohydrin which is oxidised by manganese dioxide to the α-cyanohemiacetal, which readily loses HCN:

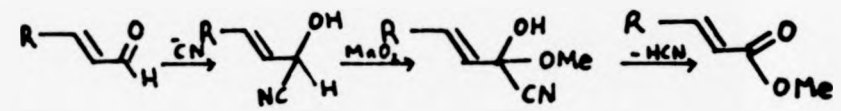


Figure 4.23

This constitutes a model synthesis of juvabione from β-turmerone; the actual synthesis was not performed owing to lack of time. The method of oxidative monofunctionalisation of 1,3-dienes may be generally applicable. β-Hydroxysulphides can be readily formed from 1,3-dienes, as shown also by reactions with trans-piperylene. In this case, the β-chlorosulphide was readily converted into a β-acetoxysulphide, as well as the β-hydroxysulphide (see section 6.8).

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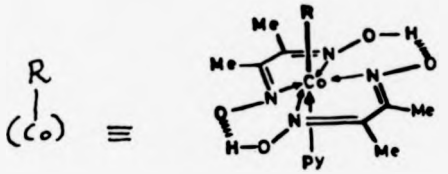

Figure 5.1 A cobaloxime. The axial base is pyridine; for hydrido cobaloxime, R=H. In this chapter, all alkylcobaloximes prepared have pyridine as axial ligand; pyridine will therefore be ommitted from the diagrams

5 Hydridocobaloximes and their Reactions

After the failure of hydrozirconation to provide the tool for monofunctionalisation of 1,3-dienes (see Chapter 3), it was decided that a cobalt species held promise as the possible reagent of choice.

It had been shown[1] that olefins could be reduced with bis(dimethylglyoximato)pyridine cobalt(II) in the presence of hydrogen. The suggestion was that co-ordination of the olefin to the cobalt was not a primary step, but that a cobalt hydride species was generated *in situ*, and it was this which reacted with the olefin[2]. The addition step was favoured by electron-withdrawing groups on the olefin. In the case of conjugated olefins, the specificity of the addition depended on the pH of the reaction medium[3]. Under basic conditions β-addition was observed, whereas under acidic conditions α-addition predominated (see fig.5.2). This observation was rationalised by Gaudemer[3] as indicating that under

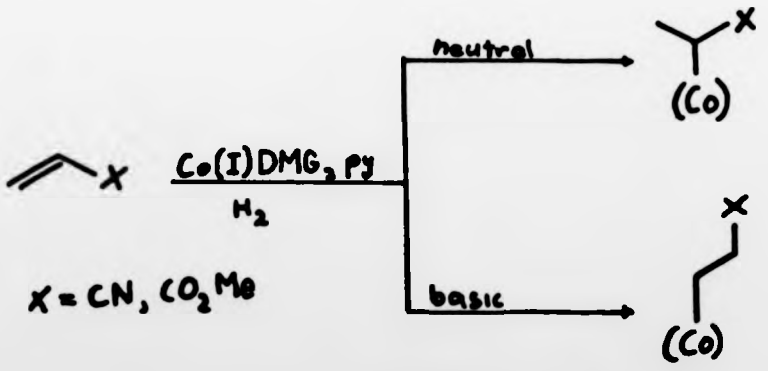

Figure 5.2 Addition to olefins[2]

neutral or acidic pH the species attacking the olefin was a hydridocobaloxime, whereas under basic conditions it was a Co(I) nucleophile that attacked the olefin. It is known that cobaloxime(I) is a powerful nucleophile, and many alkylcobalt species have been prepared by the reaction of cobaloxime(I) with suitable alkylating agents[4].

Schrauzer and Holland[5] claimed to have isolated a crystalline hydridocobaloxime with tributylphosphine as an axial ligand, instead of pyridine, by reduction of the corresponding chlorocobaloxime with sodium borohydride. The compound presents an absorption in the ^{1}HNMR at 6.0ppm in hexane, which the authors assign to the hydride species. This chemical shift is untypical of metal hydrides. Some values determined for other hydrides are[6,11]:

Hydride	(ppm)
$CoH(CO)_4$	-10.2
$CoH(PF_3)_4$	-12.5
$CoH(CN)_5^{3-}$	-12.6
$MoH(C_5H_5)(CO)_3$	- 5.7
$MnH(CO)_5$	- 7.7
$PtHCl(PEt_3)_2$	-16.9

Unfortunately, the authors do not report ^{1}HNMR data on other hydridocobaloximes they claimed to have prepared.

Gaudemer[7] reported that the thermal decomposition of (2-hydroxyphenylethyl)pyridine cobaloxime gave rise to the corresponding cobalt hydride. This occurred with transfer of hydrogen from the alkyl chain, α- to the hydroxy group, as demonstrated by deuterium labeling. No ^{1}HNMR data were given for the hydride.

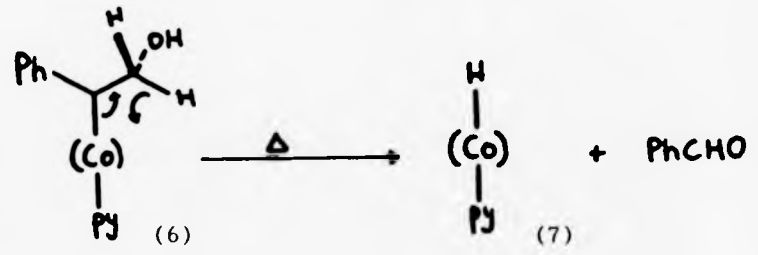

Figure 5.3

In the light of these observations, we decided to follow the thermal decomposition of (2-hydroxyphenylethyl)pyridine cobaloxime (6) by ^{1}HNMR. As expected, at 40° in D_6DMSO, the absorptions due to phenylacetaldehyde were observed (9.5ppm -CHO) to grow rapidly. Twenty minutes later, a broad absoption at -3.0ppm had appeared. This peak became sharper, and remained clearly visible until air was allowed to enter the system, after which it rapidly disappeared. This peak was thought to be due to a metal-hydride species. Its intensity was anomalously high, however, and cannot yet be satisfactorily explained. A similar absorption has been observed[8] in the thermal decomposition of a fresh batch of the same compound (6) in CD_3NO_2. Further studies are being actively pursued[8], and it is hoped that this species will be conclusively identified.

We followed the above with an experiment in which the thermal decomposition of cobaloxime (6) was performed in the presence of 2,3-dimethylbuta-1,3-diene. Although the cobaloxime (6) decomposed, no change in the 2,3-dimethylbuta-1,3-diene could be observed. Only unchanged diene was isolated from the reaction. This was surprising, because Schrauzer[9] had synthesised crotylpyridinatocobaloxime from butadiene and a mixture purported to contain

hydridocobaloxime. No alkylcobaloxime was detected either when cobaloxime (6) was decomposed in the presence of 4,4-dimethyl-1-methylenecyclohex-2-ene; however, partial isomerisation of the substrate to the endocyclic diene was observed. When cobaloxime (6)

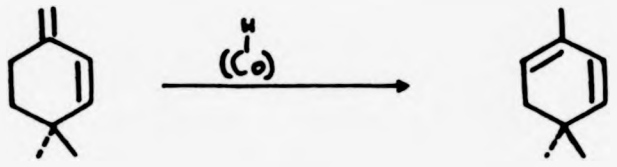

Figure 5.4

was thermolysed in the presence of methyl acrylate, however, a methyl doublet at 0.38ppm appeared after 15min at 45°. The product was shown to be 1-carboxymethylethyl(pyridine)cobaloxime:

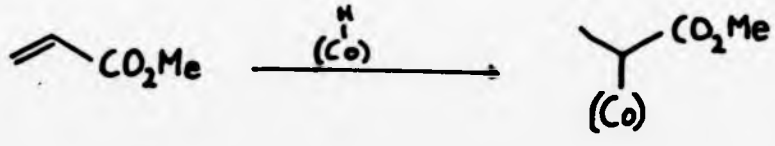

Figure 5.5

By using this same procedure, thermolysis of cobaloxime (6) in the presence of methyl penta-2,4-dienoate, a crystalline alkylcobaloxime was isolated, which was shown to be the peroxy compound produced by oxygen insertion into the Co-C bond (see fig.5.6)[10].

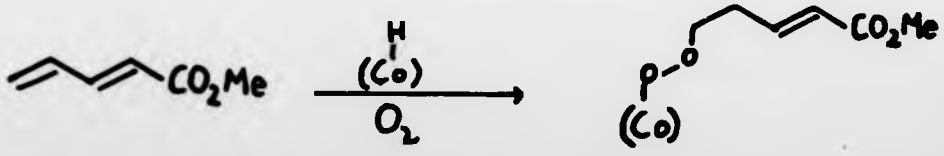

Figure 5.6

It became clear that the procedure could generate alkylcobaloximes from olefins and dienes bearing electron-withdrawing substituents. In an attempt to increase the reactivity of olefins towards this hydridocobaloxime, the addition of silver(I) and Pd(II) was attempted.

When silver(I)perchlorate was dissolved in CD_3OD with 4,4-dimethyl-1-methylenecyclohex-2-ene, the olefinic absorptions in the ^{1}HNMR shifted, indicating co-ordination had occurred. Addition of cobaloxime (6), and heating for 15min at 45°C resulted in the deposition of a fine silver mirror on the walls of the NMR tube; no alkylcobaloxime was detected, but the cobaloxime (6) was destroyed; obviously metal electron-transfer redox processes were occurring. Similar disappointing results were obtained with $(MeCN)_2PdCl_2$.

In summary, it was shown that the hydridocobaloxime which was generated by the thermal decomposition of cobaloxime (6) would react with electron-poor olefins, but not with unactivated mono-olefins or dienes. The reactivity of hydridocobaloximes might be greatly affected by the choice of axial base; instead of pyridine, cyano- or nitro- pyridines might enhance the reactivity of the corresponding hydridocobaloximes towards unactivated olefins. In our preliminary explorations, many more questions arose than could be successfully answered. The results are significant, though necessarily incomplete.

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6 Experimental

6.1 General Remarks : Materials and Methods

Selected solvents[1-8] and reagents[9] were purified by standard procedures. Oxygen-free nitrogen and argon were dried by passing through a column of Drierite. Flash chromatography refers to the technique described by Still[14] for short-column medium pressure chromatography. Petroleum refers to light petroleum-ether, b.p. 40-60°C.

NMR spectra refer to solutions in deuteriochloroform, using tetramethylsilane as internal standard, unless otherwise indicated. These were recorded on the following instruments: Hitachi-Perkin Elmer R24B, Perkin Elmer R12 and R34, Varian EM360 and Bruker WH400[a] and WH300[b]. Mass spectra were recorded on a Kratos MS80[a] or an AEIMS9[b] spectrometer. The GC/MS analysis of curcuma oil was performed at PPF International (Ashford) with a capillary free-fatty acid phase column (WCOT). Other GC analyses were obtained using a Perkin Elmer F11 or a Pye Unicam 104 gas chromatograph. HPLC work was carried out using a Gilson 303 Instrument with a Holochrome variable-wavelength UV detector or a Waters liquid chromatograph with a refractive index detector or a fixed wavelength (254 or 280nm) UV detector. Elemental analyses were obtained[b] with a Carlo Erba 1106 elemental analyser.

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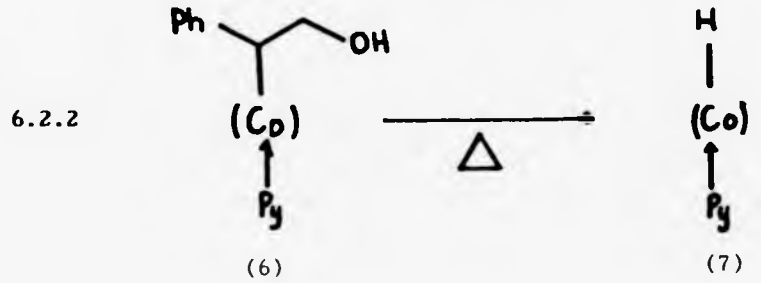
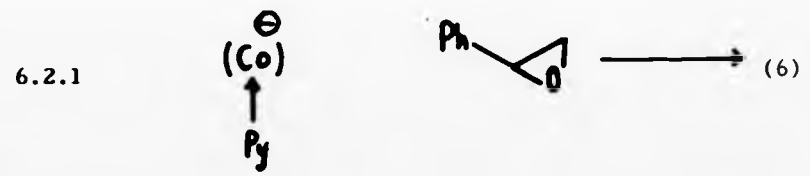
a Services of the University of Warwick. These spectra were provided by O.Howarth, E.M.Curzon and I.Katyal.

b. Services of the University of Newcastle upon Tyne. These were provided by S.Hill, I.McKeag, D.Dunbar, P.Kelly and S.Addison.





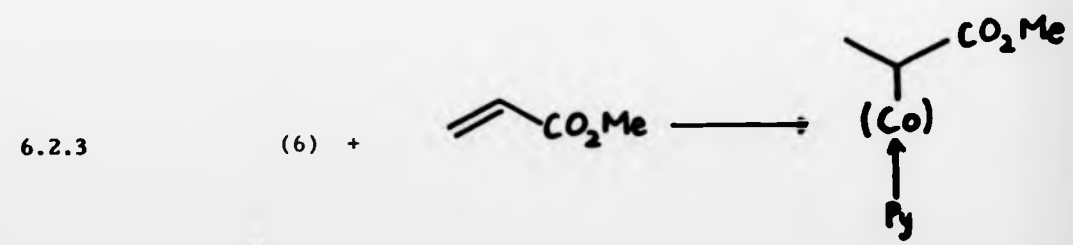
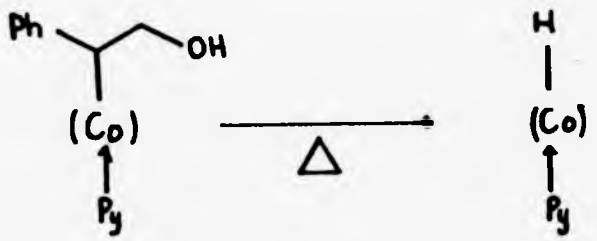


Figure 6.1 Section 6.2

6.2.2



(6) (7)

6.2.1

6.2.3

Figure 6.1 Section 6.2

6.2 Reactions of Hydridocobaloxime (7)

6.2.1 (2-Hydroxy-1-phenylethyl)pyridinecobaloxime[15, 16] (6)

A solution of bromopyridinecobaloxime[17](1)(1.8g,4.0mmol) in methanol (15ml) was degassed by vigorous stirring (30min) under nitrogen. Sodium borohydride (0.12g,3.2mmol) was added in small portions until the presence of cobaloxime-(I) was indicated (deep green colour). The mixture was then cooled to 0°C, styrene oxide (1.05g,1.0ml,8.7mmol) was added and the mixture stirred for a further hour at 0°C. The ice-bath was then removed, and sodium borohydride (1.5g,3.8mmol) added until the green colour reappeared. The mixture was cooled to 0°C (10min), allowed to warm to room temperature and then left to stand for 1h, after which ice-cold water (40ml) was added to the now dark red solution. A crimson solid precipitated, which was filtered off under nitrogen. It was washed with water, then with petroleum, and dried under vacuum in a desiccator to give the title compound (1.22g,61%), identical with that reported by Gaudemer et al[15] by proton NMR spectroscopy.

6.2.2 Thermal Decomposition[18] of (2-Hydroxy-1-phenylethyl)-pyridinecobaloxime (6)

(2-Hydroxy-1-phenylethyl)pyridinecobaloxime (6) (0.030g, 0.06mmol) was dissolved in degassed dimethylsulphoxide-d_6, and the solution transferred to a dry, nitrogen-flushed NMR tube. The tube was heated at 40°C for 3h in the probe of a Perkin Elmer R34 NMR spectrometer. Ten spectra were recorded at

5min intervals, and then every 15min. After 20min, an absorption at δ=-3.0ppm became apparent; this peak attained maximum intensity after 70min, and then declined rapidly to disappear completely within 30min. Concomitant to the appearance of the peak at δ=-3.0ppm, a peak at 9.2ppm was observed to appear, corresponding to the aldehyde proton of phenylacetaldehyde. The peak at δ=-3.0ppm was assigned to a cobalt-hydride species (7).

6.2.3 Reaction of Hydridocobaloxime (7) with Methylacrylate; 1-(Carboxymethyl)-ethylpyridinecobaloxime (8)

Freshly distilled methyl acrylate (0.09g,1.1mmol) was dissolved in dichloromethane (100ml) and the solution was degassed by stirring under nitrogen (10min). (2-Hydroxy-1-phenylethyl)pyridinecobaloxime (7)(0.49g,1.0mmol) was added, and the mixture heated at 45°C (1h). The solvent was evaporated and the residue dissolved in a minimum quantity of dichloromethane. Petroleum was added dropwise until some precipitation of desalkylcobaloxime was observed. The solution was then filtered, and further precipitation was induced by addition of petroleum. This procedure was repeated until TLC on silica gel (MEOH-CH_2Cl_2-pyridine, 5:100:1) showed no desalkylcobaloxime was present in the filtrate, and only pure 1-(carboxymethyl)ethylpyridinecobaloxime remained. The filtrate was then evaporated, to yield the title compound as an orange-yellow solid (0.118g,26%).

^{1}HNMR	(220MHz)	0.40	d	J12Hz	3H(CH_3)
		2.20	s		12H(4 x CH_3)
		3.48	s		3H(OCH_3)
		7.30	m		2H(py-)
		7.70	m		1H(py-)
		8.50	d		2H(py-)

Section 6.3

6.3.1 $PhSCl + CH_2=C(CH_3)C(CH_3)=CH_2 \longrightarrow PhSCH_2\underset{\displaystyle Cl}{\underset{|}{C}}(CH_3)C(CH_3)=CH_2$

(9)

6.3.2 $(9) + MeOH + [NaBH_4] \longrightarrow PhSCH_2\underset{\displaystyle CH_3O}{\underset{|}{C}}(CH_3)C(CH_3)=CH_2$

(10)

6.3.3 $(9) + NaOH + H_2O \longrightarrow PhSCH_2\underset{\displaystyle HO}{\underset{|}{C}}(CH_3)C(CH_3)=CH_2$

(11)

6.3.4 $(9) + NaBH_4 \xrightarrow[DMF]{80^\circ} PhSCH_2CH(CH_3)C(CH_3)=CH_2$

(12)

+

$PhSCH_2C(CH_3)=C(CH_3)_2$

(13)

6.3.5 $(9) + Bu_4^+N^+BH_4 \longrightarrow (12) + (13)$

6.3.6 $(9) \longrightarrow PhSCH_2C(CH_3)=C(CH_3)CH_2Cl$

(14)

6.3.7 $(14) + LiEt_3BH \longrightarrow (13)$

6.3.8 $(13) + NaIO_4 \longrightarrow PhS(O)CH_2C(CH_3)=C(CH_3)_2$

(15)

6.3.9 $(13) + NaIO_4 \longrightarrow (15) + PhS(O)_2CH_2C(CH_3)=C(CH_3)_2$

(16)

Figure 6.2

6.3.10 (15) + $(CF_3CO)_2O$ ⟶ (21)

6.3.11 (9) + CH_3ONa ⟶ (10)

6.3.12 (9) + CH_3CO_2Na ⟶ $PhSCH_2C(CH_3)C(CH_3)=CH_2$ with CH_3CO_2 on the C

(39)

6.3.13 (9) + KCN ⟶ $PhSCH_2C(CH_3)C(CH_3)=CH_2$ with NC on the C

(17)

6.3.14 (9) + H_2O + Ag_2O ⟶ (11)

6.3.15 (11) + $(CH_3)_3O^+BF_4^-$ ⟶ $Ph^+S(CH_3)CH_2C(CH_3)C(CH_3)=CH_2$ with $^-BF_4$ and HO on the C

(18)

NaH

$OCHC(CH_3)=C(CH_3)_2$ ⟵ (CF_3CO_2H) H_2C–(epoxide)–$C(CH_3)C(CH_3)=CH_2$

(20) (19)

6.3.16 (9) + DBU ⟶ $PhSCH=C(CH_3)C(CH_3)=CH_2$

(21)

Figure 6.3

6.3 Reactions of Sulphenyl Halides and Their Derivatives

6.3.1 Addition of Phenylsulphenyl Chloride[19] to 2,3-Dimethylbutadiene

N-Chlorosuccinimide (1.21g,9.0mmol) was suspended in dry dichloromethane (10ml) at room temperature, in a round-bottomed flask filled with a rubber septum. Thiophenol (0.99g,0.93ml,9.0mmol) was added to the stirred solution, a few drops at first until a yellow coloration appeared indicating that the reaction had been initiated. The remaining thiophenol was added over 30min with vigorous stirring at 0°C, and the resulting suspension was stirred for a further 30min at room temperature. This suspension was judged to contain 9.0mmol phenylsulphenyl chloride, and was added to a cold (-78°C) solution of 2,3-dimethylbutadiene (0.82g,9.0mmol) in dichloromethane (10ml). After the addition, the mixture was allowed to warm to 20°C, and the solvent evaporated to give a residue which was extracted with CCl_4. The extract was stirred for 30min to complete the precipitation of succinimide, and filtered. The filtrate was concentrated to give 2-chloro-2,3-dimethyl-1-phenylthiobut-3-ene as a pale yellow oil (1.91g,93.6%).

^{1}HNMR (220MHz ,CCl_4)	1.79	s		3H(CH_3)
	1.80	s		3H(CH_3)
	3.35	d	J13Hz	1H(CH_2)
	3.53	d	J13Hz	1H(CH_2)
	4.95	s		1H(=CH_2)
	5.09	s		1H(=CH_2)
	7.1-7.45	m		5H(Ph)

MS m/z 226.0575 [M+], expected for $C_{12}H_{15}SCl$: 226.0583, 191[$C_{12}H_{15}S^+$] 110[$PhSH^+$].

6.3.2 Attempted Reduction of 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)

2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)(1.90g, 8.4mmol) was slowly added to a solution of sodium borohydride (0.75g,20mmol) in methanol (20ml) with vigorous stirring at 0°C. The reaction mixture was allowed to warm to 20°C, stirred for 30min and extracted with dichloromethane (3 x 100ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 2-methoxy-2,3-dimethyl-1-(phenylthio)but-3-ene (1.6g,86%) identical by ^{1}HNMR and MS to that prepared by reaction of the chloride (9) with sodium methoxide in methanol (vide infra).

^{1}HNMR* (220MHz,CCl_4)	1.38	s		3H(CH_3)
	1.68	s		3H(CH_3)
	3.03	s		3H(OCH_3)
	3.08	s		2H(CH_2)
	5.00	d	J1.2Hz	2H(=CH_2)
	7.3	m		5H(Ph)

MS m/z 222.1084 [M+], expected for $C_{13}H_{18}OS$: 222.1078, 191 [M^+-MeO].

6.3.3 Hydrolysis of 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)

A solution of 2-chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9) (0.68g, 3.0mmol) in dioxan (5 ml) was added dropwise to

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* N.B. at 60MHz, in CCl_4, CH_3O and CH_2 are isochronous; in $CDCl_3$ they are resolved.

a vigorously stirred mixture of 3M aq NaOH (1ml), water (3ml) and dioxan (5ml). After 3h, water (100ml) was added. The mixture was saturated with sodium chloride and extracted with dichloromethane (10 x 30ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give crude 2,3-dimethyl-2-hydroxy-1-(phenylthio)but-3-ene (11)(0.45g,72%) as a light yellow oil. An analytical sample was obtained by preparative TLC on silica gel in CH_2Cl_2-petroleum-triethylamine (8:90:1).

^{1}HNMR (220MHz,CCl_4)				
	1.32	s		3H(CH_3)
	1.72	s		3H(CH_3)
	2.48	s,b		1H(OH)
	3.02	d	J14Hz	1H(CH_2)
	3.29	d	J14Hz	1H(CH_2)
	4.80	s	$W_{\frac{1}{2}}$7.3Hz	1H(=CH_2)
	5.05	s	$W_{\frac{1}{2}}$4.8Hz	1H(=CH_2)
	7.28	m		5H(Ph)

MS m/z 208.0924 [M^+], expected for $C_{12}H_{16}OS$: 208.0922.

6.3.4 Reduction of 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene[21] (9)

Sodium borohydride (0.54g,14.1mmol) was suspended in dry dimethylformamide (70ml) and the mixture was heated to 80°C. 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (6.27g,27.5mmol) was added dropwise over 15min and the reaction mixture was stirred at 80°C for 3h. Water (50ml) was added, and the mixture was extracted with pentane (3 x 30ml). The organic extracts were combined and washed with brine (4 x 20ml), dried ($MgSO_4$) and evaporated to give 4.93g (93%) of crude material. Analysis by TLC on silica gel in petroleum-ether-triethylamine (100:10:1) showed two main constituents of a complex mixture. Analytical samples

of the major components were obtained by preparative TLC (20 x 20cm plate) on silica gel 60 in CH_2Cl_2-petroleum-Et_3N (10:90:1).

Product A: 2,3-dimethyl-1-(phenylthio)but-3-ene

^{1}HNMR (220MHz,CCl_4)	1.12	d	J7Hz	3H(CH_3)
	1.70	s		3H(CH_3)
	2.75	dd	J7,14Hz	1H(CH_2)
	3.00	dd	J12,14Hz	1H(CH_2)
	4.71	s		2H(=CH_2)
	7.2	m		5H(Ph)

MS EI:m/z 192.0956 [M^+] expected for $C_{12}H_{16}S$: 192.0957. 192 [M^+], 123 [$PhSCH_2^+$], 110 [$PhSH^+$], 83 [$C_6H_{11}^+$]. $^+$CI, reagent ammonia, m/z 193 [MH^+], 123 [$PhSCH_2^+$], 83 [$C_6H_{11}^+$].

Product B: 2,3-dimethyl-1-(phenylthio)but-2-ene. This product was identical to that prepared by reduction of 4-chloro-2,3-dimethyl-1-(phenylthio)but-2-ene with lithium triethylborohydride (Section 6.3.7).

^{1}HNMR (220MHz, CCl_4)	1.53	s	3H(CH_3)
	1.65	s	3H(CH_3)
	1.78	s	3H(CH_3)
	3.50	s	2H(CH_2)
	7.20	m	5H(Ph)

In addition to the "products A and B", some 2,3-dimethyl-1-(phenylthio)buta-1,3-diene was tentatively identified in the crude product (^{1}HNMR, 220MHz, =CH_2-Ph δ =6.3ppm, s). This was not isolated. Comparison of these ^{1}HNMR spectra with that of the crude material showed the combined yield of product A and B to be approximately 60%.

6.3.5 Reduction of 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9) with tetra-n-butylammonium borohydride[22]

2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)(0.090g,

0.39mmol) and tetra-n-butylammonium borohydride (0.10g,0.39mmol) were dissolved in CD_3CN (0.5ml) in a 5mm NMR tube and the reaction was followed by ^{1}HNMR.

Starting material:

^{1}HNMR (60MHz, CD_3CN)	1.1	s	6H(2 x CH_3)
	3.45	s	2H(CH_2)
	4.90	s	1H(=CH_2)
	5.05	s	1H(=CH_2)
	7.1	m	5H(Ph)

3h after the addition of 1 equivalent, the absorptions at 1.1 and 3.45ppm showed substantial broadening, whereas there was no relative change in those at 7.1, 5.05 and 4.90ppm. The reaction mixture was then washed with water (4 x 15ml) and dried ($MgSO_4$). The ^{1}HNMR spectrum of the solution was now seen to be consistent with that of a 2:1.5 mixture of 2,3-dimethyl-1-(phenylthio)but-2-ene and 2,3-dimethyl-1-(phenylthio)but-3-ene.

6.3.6 Rearrangement of 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)

6.3.6.1 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene was distilled (Kugelrohr, oven temp. 96-135°C/0.05mmHg). The ^{1}HNMR spectrum of the distillate showed no olefinic protons, indicating complete rearrangement into 1-chloro-2,3-dimethyl-4-(phenylthio)but-2-ene (14)(60%).

6.3.6.2 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene was left at room temperature for 1 month, after which time rearrangement to 1-chloro-2,3-dimethyl-4-(phenylthio)but-2-ene was complete. The crude oil was distilled (Kugelrohr) to give (14) as a colourless oil (97%).

6.3.6.3 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (0.05g, 0.2mmol) was dissolved in CD_3CN (0.5ml) and degassed with a stream of dry nitrogen, in a 5mm NMR tube fitted with a rubber septum. The tube was incubated at 40°C and ^{1}HNMR spectra were taken at intervals. After 90h, the rearrangement was complete, as evidenced by disappearance of the absorptions in the olefinic region of the spectra. Based on the final ^{1}HNMR spectrum of the series, we concluded that the product consisted of a 1:1 mixture of (E) and (Z)-1-chloro-2,3-dimethyl-4-(phenylthio)but-2-ene (14).

The ^{1}HNMR of products of experiments 6.3.6.1, 6.3.6.2 and 6.3.6.3 were similar, indicating a mixture of E and Z isomers was present but in varying proportions depending on the method of preparation. Assignments of the spectra were obtained from these mixtures; the corresponding absorptions can be assigned to each compound, although the absolute stereochemistry about the double bond has not been determined.

Isomer 1:

^{1}HNMR (60MHz)	1.85	s	3H(CH_3)
	1.90	s	3H(CH_3)
	3.45	s	2H(CH_2-SR)
	3.95	s	2H(CH_2-Cl)
	7.1	m	5H(Ph)

Isomer 2:

^{1}HNMR (60MHz)	1.75	s	3H(CH_3)
	1.95	s	3H(CH_3)
	3.50	s	2H(CH_2-SR)
	3.75	s	2H(CH_2-Cl)
	7.1	m	5H(Ph)

Calculated shift for methylene protons next to a chlorine and a double bond[32] (=C-CH_2-Cl).

$$\delta = 0.23 + \sum \mathcal{A}(\delta)$$

$\mathcal{A}(\delta)$ for CH_2-Cl = 2.53

$\mathcal{A}(\delta)$ for $R_2C = C-CH_2$ = 1.32

δ = 0.23 + 2.53 + 1.32 = 4.08 (found 3.95 and 3.75ppm)

MS (of mixture) 226[M^+] 110[$PhSH^+$]

6.3.7 Reduction of 1-Chloro-2,3-dimethyl-4-(phenylthio)but-2-ene (14) with Lithium Triethylborohydride[23,24]

A dry reaction flask fitted with magnetic follower, reflux condenser and an inlet for dry nitrogen was immersed in a water bath at 25°C, charged with 1M lithium triethylborohydride in tetrahydrofuran (5.46ml). To this was added a solution of 1-chloro-2,3-dimethyl-4-(phenylthio)but-2-ene (0.62g,2.7mmol) in THF (3ml). The mixture was stirred for 3h at 25°C. Water (10ml) was then added, and the product was extracted into petroleum (5 x 30ml). The combined extracts were dried ($MgSO_4$) and evaporated to give 0.46g (87%) of crude 2,3-dimethyl-1-(phenylthio)but-2-ene, which was distilled (Kugelrohr, 0.1mmHg oven temp. 135°C) to give 0.44g (83%) of the product as a colourless oil.

^{1}HNMR (60MHz,CCl_4)	1.49	s	3H(CH_3)
	1.58	s	3H(CH_3)
	1.72	s	3H(CH_3)
	3.40	s	2H(CH_2)
	7.0	m	5H(Ph)

MS m/z 192[M^+] 110[$PhSH^+$] 83[$C_6H_{11}^+$]

6.3.8 Oxidation of 2,3-Dimethyl-1-(phenylthio)but-2-ene (13) with Sodium Metaperiodate[25-27]

A solution of 2,3-dimethyl-1-(phenylthio)but-2-ene (0.18g, 0.95mmol) in methanol (2ml) was added dropwise to an aqueous

solution (2ml) of sodium metaperiodate (0.22g,1.04mmol) at 0°C. The mixture was stirred (3h) at 0°C and then at 20°C (18h), after which it was extracted with dichloromethane (3 x 10ml). The combined extracts were dried ($MgSO_4$) and evaporated to give 0.144g (73%) of 2-methyl-3-(phenylsulphinylmethyl)but-2-ene (15).

^{1}HNMR (220MHz,CCl_4)	1.48	s		3H(CH_3)
	1.70	s		6H(2 x CH_3)
	3.30	d	J17Hz	1H(CH_2)
	3.57	d	J17Hz	1H(CH_2)
	7.48	m		5H(Ph)

MS m/z 208[M^+] 126[$PhS(O)^+$] 83[$C_6H_{11}^+$]

IR 1045 S=O

6.3.9 Oxidation of 2,3-Dimethyl-1-(phenylthio)but-2-ene (13) with excess Sodium Metaperiodate

A solution of sodium metaperiodate (19.6g,92mmol) in water (150ml) was cooled to 0°C. To this was added dropwise to a solution of 2,3-dimethyl-1-(phenylthio)but-2-ene (8.84g,46mmol) in ethanol (150ml) and the resulting mixture was stirred for 1h at 0°C, and 20h at room temperature. The mixture was extracted with petroleum (4 x 50ml) and the combined extracts were dried ($MgSO_4$) and evaporated to give a 2:3 mixture of 2,3-dimethyl-1-(phenylsulphinyl)but-2-ene (15) and 2,3-dimethyl-1-(phenylsulphonyl)but-2-ene (16)(8.30g). TLC on silica gel in CH_2Cl_2 (stained with iodine): Rf 0.16 (sulphoxide), 0.40 (sulphone). In the same system, 2,3-dimethyl-1-(phenylthio)but-2-ene has an Rf of 0.75. In CH_2Cl_2-ethyl acetate (1:1), the corresponding Rf values are 0.23 (sulphoxide), 0.46 (sulphone) and 0.88 (sulphide).

The crude mixture was dissolved in dichloromethane at 0°C and petroleum was added to induce crystallisation. Further recrystalisation (2 x) from dichloromethane gave 2,3-dimethyl-1-(phenylsulphonyl)but-2-ene (16)(3.67g,35%) as a crystalline solid, m.p. 93-94°C.

^{1}HNMR (60MHz)	1.28	s	3H(CH_3)
	1.60	s	3H(CH_3)
	1.75	s	3H(CH_3)
	3.79	s	2H(CH_2)
	7.5	m	5H(Ph)

MS m/z 224.0871 [M^+], expected for $C_{12}H_{16}SO_2$: 224.0871; 83 [$C_6H_{11}^+$]

IR 1665 w c=c, 1378 m-$S(O)_2$

The mother liquors were evaporated, and the yellow oil was distilled (Kugelrohr, 0.01mmHg, oven temp. 138°C) to give 2,3-dimethyl-1-(phenylsulphinyl)but-2-ene (15)(1.91g,20%) identical to that obtained in experiment 6.3.8.

6.3.10 Attempted Pummerer Rearrangement of 2,3-Dimethyl-1-(phenylsulphinyl)but-2-ene (15)

2,3-Dimethyl-1-(phenylsulphinyl)but-2-ene (15)(55mg,0.26mmol) was dissolved in dichloromethane (5ml), cooled to -78°C, and stirred under dry nitrogen (10min). Trifluoroacetic anhydride (55mg,37µl, 0.26mmol) was added dropwise, *via* syringe, over 10min, and the reaction mixture was stirred for 20min. The mixture was allowed to warm to room temperature, washed with saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to give a light yellow oil (0.029g).

^{1}HNMR presents inter alia:

(60MHz)	1.9	s	3H(CH_3)
	4.8	s	1H(=CH_2)
	4.9	s	1H(=CH_2)
	6.2	s	1H(=CH-S)

and no peaks in the region 8-12ppm (i.e. no aldehyde).

A sample of 2,3-dimethyl-1-(phenylthio)buta-1,3-diene was isolated by preparative TLC. This was identical (TLC, ^{1}HNMR) to that prepared in experiment 6.3.16. From the ^{1}HNMR of the crude material, this product constituted 50-60% of the products. No other products were identified.

6.3.11 2,3-Dimethyl-2-methoxy-1-(phenylthio)but-3-ene (10)

2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)(0.21g, 0.94mmol) was added dropwise to a rapidly stirred solution of sodium methoxide (0.056g,1.03mmol) in methanol (1ml) under nitrogen. The solution was then stirred for 24h at room temperature. The reaction mixture was poured into water (30ml), and extracted with petroleum (5 x 80ml). The extracts were washed with brine (3 x 10ml), dried ($MgSO_4$), and evaporated to give the title compound (10) as a colourless oil (0.20g,98%).

^{1}HNMR (220MHz,CCl_4)*	1.38	s		3H(CH_3)
	1.68	s		3H(CH_3)
	3.03	s		3H(CH_3O)
	3.08	s		2H(CH_2)
	5.00	d	J1.2Hz	2H(=CH_2)
	7.3	m		5H(Ph)

MS m/z 222.1084, expected for $C_{13}H_{18}OS$: 222.1078 198[$C_{12}H_{15}S^+$]

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* In $CDCl_3$ the diastereotopic methylene protons are resolved into an AB quartet.

6.3.12 2-Acetoxy-2,3-dimethyl-1-(phenylthio)but-3-ene (16)

2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)(0.21g, 0.91mmol) was dissolved in glacial acetic acid (1ml), and potassium acetate (0.15g,1.5mmol) was added. The mixture was stirred at 20°C (44h), then poured into water (50ml), and extracted with petroleum (3 x 50ml). The extracts were washed sequentially with saturated aqueous sodium bicarbonate solution (10ml) and brine (2 x 20ml), dried ($MgSO_4$) and evaporated to give 2-acetoxy-2,3-dimethyl-1-(phenylthio)but-3-ene (0.21g,93%).

^{1}HNMR (60MHz)	1.60	s		3H(CH_3)
	1.70	s		3H(CH_3)
	1.80	s		3H(CH_3)
	3.25	d	^{2}J12Hz	1H(CH_2)
	3.50	d	^{2}J12Hz	1H(CH_2)
	4.80	s		2H(=CH_2)
	7.1	m		5H(Ph)

MS m/z 250.1040 [M^+], expected for $C_{14}H_{18}O_2S$: 250.1027;

208[$C_{12}H_{15}OS^+$] 190[$C_{12}H_{13}S^+$] 123[$PhSCH_2^+$]

110[$PhSH^+$] 83[$C_6H_{11}^+$]

IR 1748,s,(C=O)

6.3.13 2-Cyano-2,3-dimethyl-1-(phenylthio)but-3-ene (17)

6.3.13.1 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)(0.24g, 1.03mmol) was added dropwise to a 1M solution of potassium cyanide in water-acetonitrile (1:1,2.5ml) and the mixture was stirred for 3h. The product was extracted into dichloromethane and the extracts were dried ($MgSO_4$) and evaporated to give a light yellow oil. TLC on silica gel (CH_2Cl_2) showed spots with Rf 0.42 and 0.63. The products were isolated by preparative TLC on silica gel (CH_2Cl_2)

and were 2,3-dimethyl-1-(phenylthio)but-3-en-1-ol (11)(0.112g,52%) [identical by ^{1}HNMR and TLC on silica gel (CH_2Cl_2), Rf: 0.42, to that prepared in experiment 6.3.3], and the title compound (17)(0.032g,14.3%) [TLC on silica gel (CH_2Cl_2) Rf: 0.63].

^{1}HNMR (60MHz)	1.50	s	3H(CH_3)
	1.75	s	3H(CH_3)
	3.15	s	2H(CH_2)
	4.95	s,b	1H(=CH_2)
	5.01	s	1H(=CH_2)
	7.1	m	5H(Ph)

6.3.13.2 A solution of 2-chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (0.33g,1.43mmol) in acetonitrile (1ml) was added to saturated aqueous potassium cyanide (1ml) and the resulting mixture was stirred at room temperature for 3 days. Product isolation as described above (5.3.13.1) gave 2-cyano-2,3-dimethyl-1-(phenylthio)but-3-ene (0.17g,55%).

^{1}HNMR: as above

MS m/z 217.0939[M^+], expected for $C_{13}H_{15}NS$: 217.0925 125[$PhSCH_2^+$], 110[$PhSH^+$]

IR 1645, m, C=CH_2 stretch; 2240, w, C=N

6.3.14 Silver-assisted Hydrolysis of 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9)

A mixture of acetonitrile (10ml) and water (10ml) was degassed by stirring under a nitrogen atmosphere (15min). Silver (I) oxide (2.83g,12.2mmol) was added to the solution contained in a flask covered with aluminium foil to exclude light. The mixture was cooled to 0°C in an ice-water bath. 2-Chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (2.52g,11.1mmol) was then added dropwise

to the vigorously stirred suspension. Stirring was continued for 1h at 0°C. The mixture was saturated with sodium chloride, filtered through Celite (3g) and extracted with petroleum (8 x 50ml). The Celite was washed with dichloromethane (2 x 10ml) and the organic extracts were combined, dried ($MgSO_4$) and the solvents were removed to give 2,3-dimethyl-1-(phenylthio)but-3-en-2-ol (1.90g, 82%) identical to a sample prepared by an alternative method (Cf. experiments 6.3.3 and 6.3.13.1) by ^{1}HNMR and TLC. Yields for this reaction varied from 68-82% depending on the reaction temperature and the efficiency of the extraction from the aqueous medium.

6.3.15 1-Methyl-1-(2-propenyl)oxirane from 2,3-Dimethyl-1-(phenylthio)but-3-en-2-ol (11)[29-31]

Trimethyloxonium tetrafluoroborate (1.10g,7.4mmol) was added to a solution of 2,3-dimethyl-1(phenylthio)but-3-en-2-ol (1.53g, 7.35mmol) in dry dichloromethane (5ml) under a nitrogen atmosphere (glove box). The solution was stirred magnetically until the salt dissolved (ca 1.5h). Sodium hydride (0.36g of a 50% dispersion in oil, i.e. 7.4mmol of pure hydride) was then added to the solution, and was allowed to react for 1h. The solvent was removed at atmospheric pressure, whilst maintaining the temperature below 45°C. The residual liquid was heated to 60°C, whereupon a fraction distilled over (0.28g of a mixture of the title epoxide and dichloromethane). However, a considerable amount of the product remaining in the flask decomposed to give a black tar.

^{1}HNMR (60MHz)	1.50	s	3H(CH_3)
	1.72	s	3H(CH_3)
	2.75	s	2H(CH_2O)
	5.1	s	CH_2Cl_2

MS m/z 98.0737[M^+], expected for $C_6H_{10}O$: 98.0732

Addition of 1 drop of trifluoroacetic acid to a sample of 1-methyl-1-(2-propenyl)oxirane (containing CH_2Cl_2, diluted with $CDCl_3$ in an NMR tube) caused appearance of absorptions due to 2,3-dimethylbut-2-en-1-al (20), which was characterised as its 2,4-dinitrophenylhydrazone (identical to that of authentic material, Cf. experiment 6.4.4).

Subsequently, no attempt was made to isolate the title epoxide by distillation and its solution in dichloromethane was treated with trifluoroacetic acid. After 1h, a freshly prepared 0.4M solution of 2,4-dinitrophenylhydrazine in 7.2M sulphuric acid[42] (10ml) was added. The mixture was stirred for 1h, and was then extracted with dichloromethane (5 x 100ml). The combined extracts were dried ($MgSO_4$) and the solvent removed. The residue was purified by chromatography on silica gel to give pure 2,4-dinitrophenylhydrazone of 2,3-dimethylbut-2-en-1-al (46%).

This preparation was repeated several times, and the recovery of the dinitrophenylhydrazone of 2,3-dimethylbut-2-en-1-al was variable, but generally low. Comparison of the ^{1}HNMR of authentic 2,3-dimethylbut-2-en-1-al with that of the product of this reaction indicated that the main component of the crude reaction product was this aldehyde. The factors which caused a low recovery of the corresponding 2,4-dinitrophenylhydrazone have not been identified.

Section 6.4

6.4.1 $(CH_3)_2CO + CH_3CH(Br)CO_2CH_3 \longrightarrow CH_3C(OH)(CH_3)C(CH_3)CO_2CH_3$

(22)

6.4.2 $(22) + POCl_3 \longrightarrow (CH_3)_2C{=}C(CH_3)CO_2CH_3$

(23)

6.4.3 $(23) + LiAlH_4 \longrightarrow (CH_3)_2C{=}C(CH_3)CH_2OH$

(24)

6.4.4 (24) + PCC ⟶ (20)

Section 6.5

6.5.1 $(CH_3S)_2 + SOCl_2 \longrightarrow 2CH_3SCl$

(25)

6.5.2 $(25) + CH_2{=}C(CH_3)C(CH_3){=}CH_2 \longrightarrow CH_3SCH_2C(CH_3)C(CH_3){=}CH_2$

(26)

$(26) + Ag_2O + H_2O \longrightarrow CH_3SCH_2C(CH_3)C(CH_3){=}CH_2$

Figure 6.4

6.3.16 2,3-Dimethyl-1-(phenylthio)buta-1,3-diene (21)[19]

1,8-Diazabiciclo[5.4.0]undec-7-ene (DBU)(3.04g,20.0mmol) was heated to 100°C, and 2,3-dimethyl-2-chloro-1-(phenylthio)but-3-ene (2.26g,10.0mmol) was added dropwise. The mixture was stirred at 100°C (10min), cooled to 20°C and diluted with 2% (w/v) HCl (50ml). A gelatinous precipitate appeared and then dissolved. The mixture was extracted with ether (3 x 50ml). The combined extracts were washed with water (25ml) and brine (25ml). After drying the ethereal solution ($MgSO_4$) and removal of the ether, a brown oil was obtained. This was distilled (Kugelrohr, 0.01mmHg, oven temperature up to 130°C) to give 2,3-dimethyl-1-(phenylthio)buta-1,3-diene as a colourless oil (1.67g,88%).

^{1}HNMR (60MHz)	1.91	s	3H(CH_3)
	2.00	s	3H(CH_3)
	4.90	s	1H(=CH_2)
	5.00	s	1H(=CH_2)
	6.30	s	1H(=CH-SR)
	7.20	s	5H(Ph)

MS 190.083 [M^+] expected for $C_{12}H_{14}S$: 190.0837, 175 [$C_{11}H_{11}S$].

6.4 Preparation of Authentic 2,3-Dimethylbut-2-en-1-al (20)

6.4.1 Methyl 2,3-dimethyl-3-hydroxybutanoate (22)[33]

Powdered zinc was activated[34] by heating to 100°C (15min) in conc. sulphuric acid containing a few drops of conc. nitric acid. After cooling to room temperature, the metal was collected by filtration under suction through a coarse glass frit. The metal was washed well with distilled water, followed by acetone, and finally with anhydrous ether. It was dried for 5h at 110°C.

A mixture of methyl 2-bromopropionate (83.5g,0.50mol), dry acetone (31.9g,40.3ml,0.50mol) and dry benzene (100ml) was placed in a dropping funnel attached to a 1l 3-necked flask fitted with a reflux condenser and containing a magnetic follower. Activated zinc powder (36.4g,0.56mol) was added to the flask. A quantity (ca 50ml) of the solution in the dropping funnel was added. The reaction mixture was stirred for 10min with gentle warming, after which a crystal of iodine was added. The addition of the solution in the dropping funnel was continued to maintain a slow reflux of the solvent. When the addition was complete, the mixture was heated to reflux for 1h, after which it was allowed to cool to room temperature. Ice-cold 20% (v/v) sulphuric acid (200ml) was added. The benzene layer was separated and the aqueous layer was extracted with benzene (2 x 25ml). The organic layers were combined, washed with cold 5% (v/v) sulphuric acid (25ml), 10% (w/v) aqueous sodium carbonate (25ml) and water (2 x 25ml). After drying the organic layer ($MgSO_4$), the benzene was removed to give a yellow oil (45.6g). This was fractionally distilled under reduced pressure to give methyl 2,3-dimethyl-3-hydroxybutanoate as a colourless liquid (34.6g,47%) b.p. 66-70°C at 12-18mmHg.

^{1}HNMR (60MHz)	1.1	d	J7Hz	3H(CH_3)
	1.2	s		6H(CH_3 x 2)
	2.5	q	J7Hz	1H(CH)
	3.0	s,b		1H(OH)
	3.6	s		3H(CH_3O)

6.4.2 Methyl 2,3-dimethylbut-2-enoate (23)

Methyl 2,3-dimethyl-hydroxybutanoate (22)(34.1g,0.23mol) was dissolved in benzene (150ml) and the solution was placed in

a round-bottomed flask fitted with a reflux condenser. Phosphorus oxychloride (38.2g,22.8ml,0.25mol) was added and the mixture was boiled under reflux for 3h. The reaction mixture was cooled and water (50ml) was added cautiously. The benzene layer was separated and was washed well with water (3 x 50ml) and brine (2 x 30ml). After drying ($MgSO_4$), most of the benzene was removed. The residual oil was fractionally distilled to give methyl 2,3-dimethylbut-2-enoate (10.84g,37%) b.p. 58°C at 12mmHg.

^{1}HNMR (60MHz)	1.75	s	6H(CH_3 x 2)
	1.95	s	3H(CH_3)
	3.65	s	3H(CH_3O)

MS m/z 128.0851 [M^+], expected for $C_7H_{12}O_7$: 128.0837;

97[$C_6H_9O^+$], 69[$C_5H_9^+$]

IR 1715 C=O, 1645 C=C

6.4.3 2,3-Dimethylbut-2-en-1-ol (24)

To a solution of 2,3-dimethylbut-2-enoate (1.28g,10mmol) in dry ether (15ml), stirred under dry nitrogen, lithium aluminium hydride (0.22g,6mmol) was added cautiously. After stirring the suspension for 1h at 20°C, water (10ml) was added cautiously, followed by 0.5M NaOH (30ml). The aqueous layer was saturated with sodium chloride, and extracted with ether (5 x 30ml). The combined extracts were washed with brine (1 x 20ml), dried ($MgSO_4$) and concentrated to give 2,3-dimethylbut-2-en-1-ol (100%) essentially pure by ^{1}HNMR spectroscopy.

^{1}HNMR (60MHz)	1.1	s	9H(CH_3 x 3)
	1.4	s	1H(OH)
	4.0	s	2H(CH_2)

MS m/z 100.0891 [M^+], expected for $C_6H_{12}O$: 100.0888

6.4.4 2,3-Dimethylbut-2-en-1-al (20)

A solution of 2,3-dimethylbut-2-en-1-ol (24)(0.66g,6.6mmol) in dichloromethane (1ml) was mixed with a suspension of pyridinium dichromate (3.73g,9.9mmol) in dichloromethane (10ml). After stirring the reaction mixture for 18h under dry argon, ether-pentane (1:1 v/v, 20ml) was added. The resulting suspension was filtered through a short column of anhydrous magnesium sulphate. The filtrate was carefully concentrated by distillation at ca 400mmHg. The residual liquid was distilled (Kugelrohr) to give 2,3-dimethylbut-2-en-1-al (0.45g,70%) as a colourless oil.

^{1}HNMR (60MHz)	1.7	s	3H(CH_3)
	2.0	s	3H(CH_3)
	2.1	s	3H(CH_3)
	9.9	s	1H(CHO)

2,4-Dinitrophenylhydrazone m.p. 197-198°C

^{1}HNMR (300MHz)	1.90	s	3H(CH_3)
	1.91	s	3H(CH_3)
	1.94	s	3H(CH_3)
	7.92	m	1H(Ar-H)
	8.25	m	2H(Ar-H)
	9.10	m	1H(N=CH-)
	11.10	s,b	1H(NH)

MS m/z 278.1020[M^+], expected for $C_{12}H_{14}N_4O_4$: 278.1015

6.5 Methanesulphenyl Chloride

6.5.1 Preparation of Methanesulphenyl Chloride (25)[35,36]

Sulphuryl chloride (34.0g,20.2ml,250mmol) was added dropwise to dimethyl disulphide (23.6g,22.5ml,250mmol) with thorough stirring, while the temperature of the mixture was maintained between -15°C

and -20°C. After the reaction mixture was stirred for 1h at -20°C, it was fractionally distilled under reduced pressure. The fraction b.p. 30-32°C at 110mmHg was collected in calibrated flasks (up to 25ml capacity) cooled to -78°C. The flasks were flushed with dry nitrogen, stoppered and allowed to warm to room temperature in a desiccator, and weighed. The desired solvent was added to give a deep yellow solution of methane sulphenyl chloride of known molarity. The flasks were sealed with a rubber septum and stored at -20°C. Before using for a reaction, an aliquot of the solution was removed by syringe and the quality of the solution was checked by ^{1}HNMR spectroscopy [δ CCl_4 2.9ppm, s,(MeSCl)]. If any other absorptions were present, the solution was disposed of by pouring into aqueous sodium hypochlorite. In general, an unused ca 0.7M solution of MeSCl in CCl_4 or CH_2Cl_2 was still pure after 7days at -20°C, if kept under nitrogen. Solutions stored for longer times or subjected to several uses showed substantial decomposition.

6.5.2 Reaction of Methanesulphenyl chloride with 2,3-Dimethylbuta-1,3-diene

A solution of 2,3-dimethylbuta-1,3-diene (1.32g,16mmol) in dichloromethane (5ml) was cooled under nitrogen to -78°C. Methanesulphenyl chloride in dichloromethane (8ml of a 2M solution) was added dropwise, ensuring that the reaction temperature remained below -60°C. The reaction occurred immediately, as was indicated by the disappearance of the deep yellow colour of methanesulphenyl chloride. Once the addition was complete, the reaction mixture was allowed to warm up to room temperature and the dichloromethane

was removed to yield crude 2-chloro-2,3-dimethyl-1-(methylthio)but-3-ene (26) as a light yellow oil.

This was added dropwise to a suspension of silver(I)oxide (3.74g,16mmol) in acetonitrile-water (1:1 v/v,10ml) under argon and maintained at 0°C. The reaction was continued for 1h at 0°C. The mixture was saturated with sodium chloride, and the suspension was filtered through Celite. The filtrate was extracted with ether (5 x 50ml) and the combined organic phases were dried ($MgSO_4$). The solvents were removed to give 2,3-dimethyl-1-(methylthio)but-3-ene-2-ol (27) (1.75g,75%), essentially pure by ^{1}HNMR spectroscopy.

^{1}HNMR (60MHz,CCl_4)	1.3	s		3H(CH_3)
	1.7	s		3H(CH_3)
	2.1	s		3H(CH_3-S)
	2.5	d	^{2}J14Hz	1H(CH_2)
	2.8	d	^{2}J14Hz	1H(CH_2)
	2.85	s		1H(OH)
	4.8	s		1H(=CH_2)
	5.0	s		1H(=CH_2)

6.6 Oxirane Opening and Closure

6.6.1 Reaction of Styrene Oxide with Sodium Thiophenoxide[43]

Sodium hydride (2.4g of a 50% dispersion in oil,50mmol) was placed in a nitrogen-flushed round-bottomed flask and washed with pentane (2 x 10ml). Dry dichloromethane (10ml) was then added, and the suspension was cooled to 0°C. Thiophenol (5.51g, 5.11ml,50mmol) was added dropwise over 10min and the reaction mixture was stirred for 3h at 0°C to complete the formation of the thiolate. Styrene oxide (6.035g,50mmol) was then added dropwise and the mixture was allowed to warm up to room temperature.

The mixture was stirred for 9h at 20°C. The resultant cream coloured suspension was washed sequentially with water (20ml), 0.5M HCl (3 x 50ml) until it became a clear yellow solution, 0.1M HCl (2 x 50ml), water (50ml); it was then dried ($MgSO_4$) and the solvent evaporated. The residue, a clear yellow oil (9.42g) was analysed by TLC on neutral alumina (petroleum-CH_2Cl_2, 3:1) and ^{1}HNMR spectroscopy. Both techniques indicated some starting material was present, and the product was purified by column chromatography on neutral alumina (petroleum-CH_2Cl_2,3:1) to give a 3:2 mixture of regioisomers (7.1g,61%). The 60MHz ^{1}HNMR spectrum shows 2 ABX systems; the ratio of regioisomers was calculated from the corresponding peak areas after exchange of the alcohol protons with D_2O was complete.

^{1}HNMR (60MHz)	3.06	q	A'B'	2H(CH_2)
	3.72	q	A^2B^2	2H(CH_2)
	4.18	dd	X^2	1H(CH)
	4.60	dd	X'	1H(CH)
	7.15	m		10H(Ph)
	3.1-3.5			2H[a](2 x OH)

6.6.2 Synthesis of Styrene Oxide

The 3:2 mixture of regioisomeric β-hydroxysulphides obtained in experiment 5.6.1 (0.55g,2.4mmol) was dissolved in dichloromethane (10ml), and the solution was stirred under nitrogen (10min). In a dry box, trimethyloxonium tetrafluoroborate (0.35g,2.4mmol) was added to the solution, and the mixture was stirred until the salt dissolved (ca 25min). Sodium hydride (0.11g of a 50% dispersion in oil,2.4mmol) was then added. When evolution of hydrogen

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[a] Integral measured by difference before and after D_2O exchange

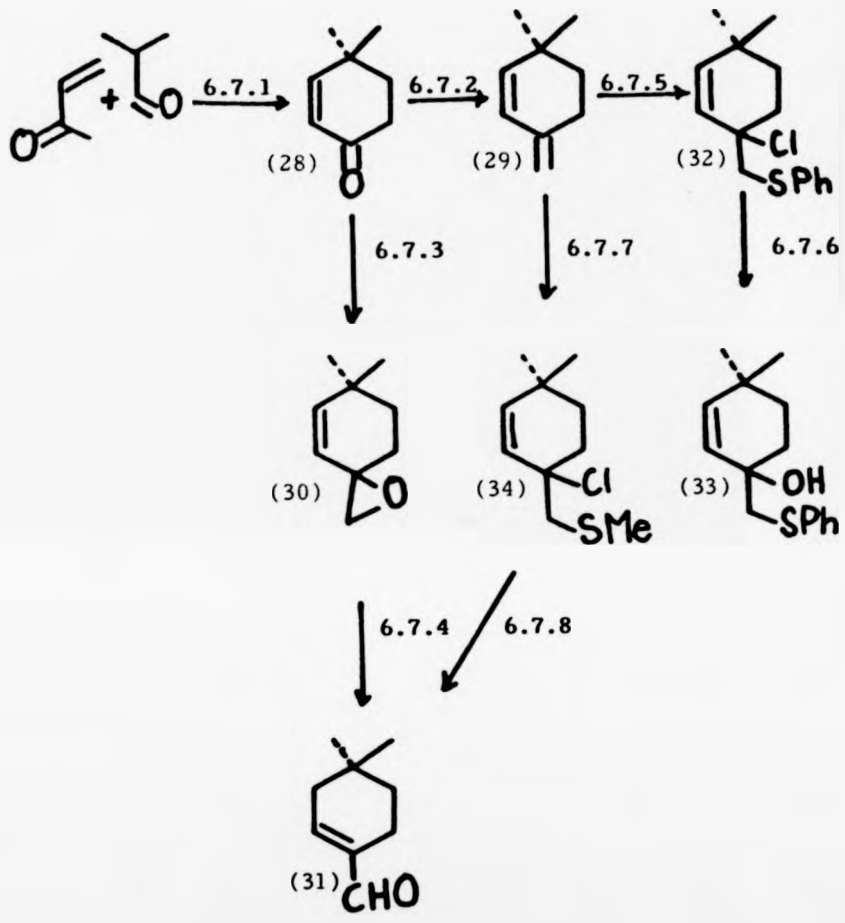

Figure 6.5 This illustration depicts the reactions of Section 6.7 (p.153-160)

subsided (15min) the mixture was washed with water (2 x 10ml), dried ($MgSO_4$), and evaporated to give a 1:1 mixture (by ^{1}HNMR) of styrene oxide and methylphenyl sulphide (0.53g,98%). Analytical samples of styrene oxide and methylphenylsulphide were obtained by preparative TLC on silica, and were identical to authentic material (^{1}HNMR, MS, TLC).

6.7 Preparation and Reactions of 4,4-Dimethyl-1-methylenecyclohex-2-ene

6.7.1 Robinson Annelation[37]: Preparation of 4,4-Dimethylcyclohex-2-en-1-one (28)

A mixture of freshly distilled methylvinylketone (70g,1mol) and isobutyraldehyde (72g,1mol) was dissolved in water (100ml) and sufficient methanol to ensure homogeneity. This solution was added slowly to a well stirred solution of potassium hydroxide (3.7g,66mmol) in methanol (20ml). During the addition, the reaction mixture was heated slowly to 75-80°C. At the end of the addition the mixture was cooled to room temperature and extracted with ether (7 x 50ml). The combined extracts were washed with brine (3 x 10ml), dried ($MgSO_4$), and the solvent evaporated. The product was fractionally distilled under reduced pressure to give the title compound (28)(30g,25%,b.p. 76-89°C at 12-22mmHg).

^{1}HNMR (60MHz,CCl_4)	1.0	s		6H(CH_3 x 2)
	1.4 - 2.2	m		4H(CH_2 x 2)
	5.6	d	J10Hz	1H(=CH)
	6.5	d	J10Hz	1H(=CH)

MS m/z 124[M^+], 109[$C_7H_9O^+$], 96[$C_6H_8O^+$]

IR 1682 C=O 1629 C=C

2,4-Dinitrophenylhydrazone: m.p. 261-262°C

^{1}HNMR (300MHz)				
	1.06	s		6H(CH_3 x 2)
	1.71	t	J6.5Hz	2H(CH_2)
	2.56	t	J6.5	2H(CH_2)
	6.11	s		2H(HC=CH)
	7.94	d	J10Hz	1H(Ar-H)
	8.22	m	J10Hz,2Hz	1H(Ar-H)
	9.07	d	J2Hz	1H(Ar-H)
	11.1	s,b		1H(N-H)

MS m/z 304[M^+]

6.7.2 4,4-Dimethyl-1-methylenecyclohex-2-ene (29)[38]

A flame-dried 3-necked flask fitted with a magnetic stirrer, condenser, thermometer and nitrogen inlet tube was placed in a water bath. A steady stream of nitrogen was passed through the flask, and was maintained throughout the reaction. Dry dimethylsulphoxide (250ml) was placed in the flask and was stirred vigorously for 30min. The condenser was briefly removed to introduce sodium hydride (9.6g of a 50% dispersion in oil,0.2mol). The mixture was warmed to 65°C until the sodium hydride dissolved (ca 1.5h). The mixture was rapidly cooled to room temperature and methyltriphenylphosphonium iodide (80.85g,0.2mol) was added in portions over 15min. The solution became dark red, and a slightly exothermic reaction ensued. The temperature was maintained at 20°C during the addition and for a further 10min. 4,4-Dimethylcyclohex-2-ene-1-one (28)(24.8g,0.2mol) was then added. The mixture was stirred at 50°C for 1h, cooled to 20°C, and extracted with petroleum (5 x 50ml). The combined extracts were washed with water (3 x 50ml), dried ($MgSO_4$) and the solvent was distilled off at atmospheric pressure. The residue was fractionally distilled

under reduced pressure to give the title compound (15.8g,65%) as a colourless liquid (b.p. 45° at 12mmHg).

^{1}HNMR (60MHz,CCl_4)	1.0	s		6H(CH_3 x 2)
	1.5	t	J6Hz	2H(CH_2)
	2.3	t	J6Hz	2H(CH_2)
	4.7	s		2H(=CH_2)
	5.4	d	J10Hz	1H(=CH)
	5.9	d	J10Hz	1H(=CH)

MS m/z 122[M^+], 107[$C_8H_{11}^+$], 91[$C_7H_7^+$]

IR 1638 w C=C, 1596 $C=CH_2$

6.7.3 6,6-Dimethyl-1-oxaspiro[2.5]oct-4-ene[40]

Trimethylsulphonium iodide was prepared according to the procedure of Corey and Chaykovsky[39], recrystallised from methanol-petroleum, and dried under vacuum (19h), m.p. 212-213°C.

Sodium hydride (0.77g of a 50% dispersion in oil,32mmol) was dissolved, under nitrogen, in a mixture of dry dimethylsulphoxide (10ml) and dry tetrahydrofuran (15ml) and the mixture was cooled to -10°C with an ice-salt bath. With continuous stirring, a solution of trimethylsulphonium iodide (6.53g,32mmol) in dimethylsulphoxide (25ml) was added over 3min. The mixture was stirred for a further 2min, ensuring that the temperature did not rise above 5°C. When the mixture reached 0°C again, a solution of 4,4-dimethylcyclohex-2-en-1-one (3.72g,30mmol) in dimethylsulphoxide (15ml) was added dropwise over 3min; the mixture was stirred for 10min at 0°C, followed by 1h at room temperature. Ice-cold water (70ml) was added to the mixture and it was extracted with pentane (3 x 50ml). The extracts were washed with water (2 x 100ml), cooled to -20°C for 6h, filtered while cold, and

dried (K_2CO_3). The solvent was then distilled off carefully at atmospheric pressure, and the residue was distilled at reduced pressure (Kugelrohr,12-20mmHg,oven temperature: 70°C) to give the title compound (30) contaminated with 4,4-dimethylcyclohex-2-en-1-one (3.31g). Comparison of the ^{1}HNMR of the product mixture with that of 4,4-dimethylcyclohex-2-en-1-one indicated the yield of epoxide (30) was ca 50%.

^{1}HNMR (60MHz)	1.0	s		3H(CH_3)
	1.02	s		3H(CH_3)
	1.5 -			
	2.0	m		4H(CH_2 x 2)
	2.7	s		2H(O=CH_2)
	5.0	d	J10Hz	1H(=CH)
	5.7	d	J10Hz	1H(=CH)

MS m/z 138[M^+]

IR 1643 C=C, 1289 symmetric epoxide stretch

6.7.4 4,4-Dimethyl-1-formylcyclohex-1-ene (31)

6,6-Dimethyl-1-oxaspiro[2.5]oct-4-ene* (1.52g,11.0mmol) was dissolved in dichloromethane (20ml) and p-toluenesulphonic acid monohydrate (3mg,1.5 x 10^{-2}mmol) was added. The reaction was followed by ^{1}HNMR spectroscopy. The signal at δ=2.7ppm disappeared within 10min, as did those at δ=5.0 and 5.7ppm. A peak appeared at δ=9.2ppm. After 5h at 20°C, no further change was apparent

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* The product from experiment 6.7.3 was used directly in this reaction, so alongside 6,6-dimethyl-1-oxaspiro[2.5]oct-4-ene (1.52g,11.0mmol) there was 4,4-dimethylcyclohex-2-en-1-one (0.81g,6.6mmol). This ketone, however, remained unchanged throughout the reaction, as could be seen from ^{1}HNMR spectroscopy and by the isolation of its 2,4-dinitrophenylhydrazone at the end of the reaction.

and the reaction mixture was washed with saturated aqueous sodium bicarbonate (2 x 10ml), dried ($MgSO_4$) and the solvent was evaporated. The residue was then distilled (Kugelrohr,oven temperature 50-60°C at 11mmHg) to give the title compound (31)(1.12g,74%).

^{1}HNMR (60MHz)	0.90	s	6H(CH_3 x 2)
	1.40	t	2H(CH_2)
	2.1	d	2H(CH_2)
	2.2	t	2H(CH_2)
	6.6	t	1H(=CH)
	9.2	s	1H(CHO)

MS m/z 138[M^+]

IR 1682 C=O

2,4-dinitrophenylhydrazone

^{1}HNMR (300MHz)	0.97	s	6H(CH_3 x 2)
	1.50	t J6Hz	2H(CH_2)
	2.07	d J<1Hz	2H(CH_2)
	2.60	t	2H(CH_2)
	7.20	s	1H(N=C-H)
	7.97	d J9Hz	1H(Ar-H)
	8.25	m	1H(=CH)
	8.28	m	1H(Ar-H)
	9.13	m	1H(Ar-H)
	11.25	s,b	1H(N-H)

MS m/z 318[M^+], 304[$C_{14}H_{16}N_4O_4^+$], 289[$C_{14}H_{13}N_4O_4^+$], 107[$C_8H_{11}^+$]

6.7.5 1-Chloro-4,4-dimethyl-1-(phenylthiomethyl)cyclohex-2-ene (32)

Phenylsulphenyl chloride (3.60g,25mmol) in dichloromethane (27ml) was prepared in the manner described (Cf experiment 6.3.1). 4,4-Dimethyl-1-methylenecyclohex-2-ene (2.05g,25mmol) was added to the sulphenyl chloride solution at -78°C. The mixture was stirred for 3min at -78°C, and was allowed to reach room temperature.

The solvent was removed, and the residue was taken up in CCl_4 (10ml). The suspension was stirred for 30min, filtered and evaporated to give the title compound as a colourless oil (5.58g,83%).

^{1}HNMR (60MHz,CCl_4)	0.90	s	6H(CH_3 x 2)
	1.0 - 2.2	m	4H(CH_2 x 2)
	3.3	s	2H(CH_2 - S)
	4.05	s,b $w_{\frac{1}{2}}$7Hz	1H(=CH)
	5.4	s,b $w_{\frac{1}{2}}$7Hz	1H(=CH)
	7.0	s	5H(Ph)

MS m/z 266.0916[M^+], expected for $C_{15}H_{19}SCl$: 266.0896

230[$C_{15}H_{19}S^+$], 121[$C_9H_{13}^+$], 77[Ph^+]

6.7.6 4,4-Dimethyl-1-hydroxy-1-(phenylthiomethyl)cyclohex-2-ene (33)

1-Chloro-4,4-dimethyl-1-(phenylthiomethyl)cyclohex-2-ene (32) (1.24g,4.6mmol) was added dropwise to a well stirred mixture of 3M sodium hydroxide (6ml) and dioxan (6ml), at 20°C. The mixture was stirred for 8h, and was saturated with sodium chloride. The mixture was then extracted with ether (3 x 20ml), and the combined organic extracts were dried ($MgSO_4$) and the solvents evaporated to give a deep yellow oil (1.1g). Analysis of this oil by TLC on silica gel (CH_2Cl_2,staining with iodine) showed four main components of a complex mixture (Rf 0.46, 0.63, 0.82 and 0.94). A sample (0.10g) of the oil was fractionated by preparative TLC on silica gel (CH_2Cl_2) and 4,4-dimethyl-1-hydroxy-1-(phenylthiomethyl)cyclohex-2-ene (33) was isolated (0.07g,70%). Column chromatography on silica gel caused substantial decomposition of the sample, with and without addition of triethylamine to the mobile phase. Column chromatography on neutral alumina (Merck 1077,

t-butylmethylether-petroleum,3:7) gave homogeneous fractions of the title compound (33)(0.77g,68%).

TLC on silica gel (CH_2Cl_2) Rf: 0.63

^{1}HNMR (60MHz)	0.99	s	3H(CH_3)
	1.02	s	3H(CH_3)
	1.2 - 2.0	m	4H(CH_2 x 2)
	2.2	s,b[a]	1H(OH)
	3.10	s[b]	2H(CH_2-S)
	5.40	s[b]	2H(HC=CH)
	7.20	m	5H(Ph)

MS m/z 248.1229[M^+], expected for $C_{15}H_{20}OS$: 248.1235

230[$C_{15}H_{18}S^+$], 215[$C_{14}H_{15}O^+$], 109[PhS^+], 77[Ph^+]

6.7.7 4,4-Dimethyl-1-hydroxy-1-(methylthiomethyl)cyclohex-2-ene (34)

4,4-Dimethyl-1-methylenecyclohex-2-ene (29)(0.43g,3.5mmol) was dissolved in dry dichloromethane and the solution was cooled to -78°C. Methylsulphenyl chloride solution (0.7M) in dichloromethane (5ml,3.5mmol) was added dropwise with thorough stirring, and while ensuring that the temperature of the reaction mixture remained below -70°C. When the addition was complete, the mixture was allowed to warm to 20°C, and the solvent was evaporated to yield a colourless oil (0.72g,100%) which was immediately added to a suspension of silver(I)oxide (0.81g,3.5mmol), water (5ml) and acetonitrile (5ml) at 0°C. The suspension was stirred for 1h, after which it was saturated with sodium chloride, diluted with

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a Exchanges with D_2O

b In C_6D_6 these protons resonate as an AB quartet at 5.30ppm

ether (50ml) and filtered through Celite (3g). The solid residue was washed with ether (3 x 50ml), and the filtrate was separated and the aqueous phase was extracted with dichloromethane (2 x 10ml). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated to give the title compound (34)(0.53g,74%) as a colourless oil.

^{1}HNMR (60MHz)	1.05	s	3H(CH_3)
	1.1	s	3H(CH_3)
	1.4 -		
	2.0	m	4H(CH_2 x 2)
	2.1	s,b[a]	1H(OH)
	2.3	s	3H(CH_3-S)
	2.8	s	2H(CH_2-S)
	5.6	s	2H(HC=CH)

MS m/z 186.1079 [M^+] expected for $C_{10}H_{18}OS$: 186.1079, 186[M^+], 168[$C_{10}H_{16}S^+$], 153[$C_9H_{13}S^+$]

6.7.8 4,4-Dimethyl-1-formylcyclohex-1-ene (31)

4,4-Dimethyl-1-hydroxy-1-(phenylthiomethyl)cyclohex-2-ene (32) (0.33g,1.32mmol) was dissolved in dry, nitrogen-flushed dichloromethane (3ml) and trimethyloxonium tetrafluoroborate (0.19g,1.31mmol) was added to the solution, under nitrogen, in a dry box. The solution was stirred until the salt dissolved (ca 4h) and sodium hydride (0.063g of a 50% dispersion in oil,1.32mmol) was added. The suspension was stirred until evolution of hydrogen ceased (0.5h). The mixture was then filtered and the filtrate was acidified with p-toluenesulphonic acid (10mg,5.8 x 10^{-5}mol) and was left for 12h at 20°C. 0.4M 2,4-dinitrophenylhydrazine solution in H_2SO_4 (175ml) was prepared as described[42], and was added to the reaction

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a exchanges in D_2O

Section 6.8

6.8.1 $CH_3CH=CHCH=CH_2 + PHSCl \longrightarrow CH_3CH=CH-\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2SPh$

(35)

6.8.2 (35) + $CH_3CO_2Na \longrightarrow CH_3CH=CH\underset{\displaystyle CH_3CO_2}{\underset{/}{C}}HCH_2SPh$

(36)

6.8.3 (35) $\longrightarrow CH_3CH=CH\underset{\displaystyle OH}{\underset{|}{C}}HCH_2SPh$

(37)

Figure 6.6

This illustration depicts the reactions

described in sections 6.8.1 - 6.8.3, on p.162-164.

mixture, which was then stirred for 6h. The mixture was then extracted with dichloromethane (6 x 50ml), and the extracts were dried ($MgSO_4$) and the solvent evaporated to give a solid residue. The residue was dissolved in ether (7ml) and the solution was diluted with petroleum (50ml). This solution was filtered through a 5cm bed of silica gel (5gm) under suction. A mixture of ether-petroleum (50ml,3:7) was passed through the silica, and the filtrate was evaporated to yield crude 2,4-dinitrophenylhydrazone of 4,4-dimethyl-1-formylcyclohex-1-ene (0.11g,26%) which was purified by preparative TLC on silica gel (ether-petroleum,1:10) to give pure 2,4-dinitrophenylhydrazone, identical (TLC, ^{1}HNMR,MS) to that from authentic material (Cf experiment 6.7.4).

6.8 Reactions with Piperylene

6.8.1 trans-2-Chloro-1-(phenylthio)pent-3-ene (35)

N-Chlorosuccinimide (1.34g,10mmol) was suspended in dichloromethane (10ml) and thiophenol (1.10g,1.02ml,10mmol) was added in the manner described above (Cf experiment 5.3.1) trans-piperylene (0.68g,10mmol) was then added to the solution of phenylsulphenyl chloride at -78°C. The suspension was left to warm to 20°C, the solvent was evaporated and the residue was suspended in CCl_4 (5ml), stirred for 30min, filtered, and the solvent was evaporated to give the title compound (35) as a light yellow oil (2.0g,97%).

^{1}HNMR (60MHz,CCl_4)	1.70	d J5Hz	3H(CH_3)
	3.20	dd(AB)	2H(CH_2-)
	4.20	ddd	1H(CH-Cl)
	5.3 - 5.7	m	2H(HC=CH)
	7.1	m	5H(Ph)

MS m/z no M^+; 176[$C_{11}H_{12}S^+$], 110[$PhSH^+$]

IR 1670 w C=C trans

6.8.2 trans-2-Acetoxy-1-(phenylthio)pent-3-ene (36)

trans-2-Chloro-1-(phenylthio)pent-3-ene (35)(1.58g,6.9mmol) was added dropwise to a vigorously stirred solution of sodium acetate (anhydrous,1.2g,20.3mmol) in acetic acid (10ml). During the addition, a white precipitate appeared. The mixture was allowed to react for 16h, and was extracted with petroleum (5 x 50ml). The combined extracts were washed with saturated aqueous sodium bicarbonate (2 x 5ml), water (5ml), and were dried ($MgSO_4$). The solvent was evaporated to give the title compound as a light yellow oil (1.62g,99%).

^{1}HNMR (60MHz,CCl_4)	1.70	d	J5Hz	3H(CH_3)
	1.90	s		3H(CH_3)
	5.0 - 5.6	m		2H(HC=CH)
	7.1	m		5H(Ph)

MS m/z 236.0904 [M^+], expected for $C_{13}H_{16}O_2S$: 236.0871;
176[$C_{11}H_{12}S^+$], 109[PhS^+]

IR 1748 s(C=O;acetate), 1675 w (C=C;trans)

6.8.3 trans-2-Hydroxy-1-(phenylthio)pent-3-ene (37)

N-Chlorosuccinimide (4.12g,30.8mmol) was suspended in dry dichloromethane (30ml) and thiophenol (3.40g,3.15ml,30.8mmol) was added dropwise to the well-stirred suspension, in the manner described above (Cf experiment 6.3.1). The resultant phenylsulphenyl chloride solution was cooled to -78°C and trans-piperylene (2.1g, 30.8mmol) was added dropwise via syringe. The suspension was

allowed to warm up to room temperature, and the solvent was evaporated. The residue was suspended in CCl_4 (5ml) and was stirred for 20min, after which it was filtered and the solvent evaporated to give a light yellow oil (6.54g,100%) which was added dropwise to a mixture of 3M sodium hydroxide (5ml) and dioxan (5ml). The mixture was stirred for 1h, and was extracted with dichloromethane (5 x 50ml). The extracts were dried ($MgSO_4$) and the solvent evaporated to give the title compound as a colourless oil (4.7g,80%).

^{1}HNMR (300MHz)	1.67	dd	^{3}J6.5Hz ^{4}J1.2Hz	(3H)(CH_3)
	2.65	s,b		1H(OH)
	2.93	dd	^{2}J13.6Hz ^{3}J7.4Hz	1H(CH_2-S)
	3.10	dd	^{2}J13.6Hz ^{3}J4.4Hz	1H(CH_2-S)
	4.13	dd	^{3}J7.4Hz ^{3}J4.4Hz	
	5.48	ddq	^{3}J15Hz ^{3}J5.5Hz ^{4}J1.2Hz	1H(HC=)
	5.71	ddq	^{3}J15Hz ^{3}J6.5Hz ^{4}J1Hz	1H(=CH-CH_3)
	7.1 - 7.4	m		5H(Ph)

MS m/z 194.0763 [M^+], expected for $C_{11}H_{14}SO$: 194.0765

109[PhS^+]

IR 3400 s,b (-OH), 1670 w (C=C)

6.9 3-Methylenecholest-4-ene[41]

6.9.1 Preparation of 3-Methylenecholest-4-ene

3-Methylenecholest-4-ene was prepared by the method of Sondheimer[41], and purified by column chromatography on silica gel (petroleum-triethylamine 99:1). Gas chromatography coupled to a mass spectrometer (WCOT column, CPSil5 liquid phase, 26M, 0.32mm id) on-column injection and an 80-300°C temperature ramp gave the following results:

Steroid	Relative Retention (t)	Best fit for M^+	Absolute error (±mmu)
5-α-androstan-17-β-ol-3-one[a]	0.00	$C_{19}H_{30}O_2$	4
3-methylenecholest-4-ene	3.18	$C_{28}H_{46}$	3.5
cholesterol[a]	4.24	$C_{27}H_{46}O$	4
cholest-4-en-3-one[a]	4.39	$C_{27}H_{46}O$	0

3-Methylenecholest-4-ene: m.p. 70-71°C (Lit 72-73°C)

^{1}HNMR	4.5	s	2H(=CH_2)

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a Introduced as internal standards

Compounds Prepared : New Compounds are Underlined

1. (2-hydroxy-1-phenylethyl)pyridinecobaloxime (6). Red solid, decomposes before melting. TLC on silica gel (EtOAc-pyridine, 99:1). One yellow spot Rf.0.20. ^{1}HNMR as in Ref.15.

2. 1-(carboxymethyl)ethylpyridinecobaloxime (8). Orange-yellow solid. TLC on silica gel (MeOH-CH_2Cl_2-pyridine 5:100:1). One yellow spot Rf.0.35. ^{1}HNMR see section 6.2.3. Similar to that reported in Ref.44.

3. 2-chloro-2,3-dimethyl-1-(phenylthio)but-3-ene (9). Pale yellow oil (cf. section 6.3.1). ^{1}HNMR, MS similar to that reported in Ref.19.

4. 2-methoxy-2,3-dimethyl-1-(phenylthio)but-3-ene (10). Colourless oil, one spot on TLC (CH_2Cl_2). ^{1}HNMR, MS see section 6.3.2.

5. 2,3-dimethyl-2-hydroxy-1-(phenylthio)but-3-ene (11). Light yellow oil. TLC on silica gel (CH_2Cl_2) one spot Rf.0.42. ^{1}HNMR, MS, see section 6.3.3.

6. 2,3-dimethyl-1-(phenylthio)but-3-ene (12). Colourless oil. TLC on silica gel (CH_2Cl_2-petroleum-Et_3N 10:90:1) one spot. ^{1}HNMR, EIMS, CIMS, see section 6.3.4.

7. 2,3-dimethyl-1-(phenylthio)but-2-ene (13). Colourless oil. TLC on silica gel (CH_2Cl_2-petroleum-Et_3N 10:90:1) one spot; (CH_2Cl_2) Rf.0.75. ^{1}HNMR, section 6.3.4 and 6.3.7. MS section 6.3.7.

8. 1-chloro-2,3-dimethyl-4-(phenylthio)but-2-ene (14). Colourless oil, bp ca.100°C @ 0.05mmHg. ^{1}HNMR, similar to that reported in ref. 45 (see section 6.3.6).

9. 2-methyl-3-(phenylsulphinylmethyl)but-2-ene (15). Colourless oil, (solidifies ca.-5°C). TLC on silica gel (CH_2Cl_2) one spot Rf.0.16. ^{1}HNMR, MS, IR: section 6.3.8.

10. 2,3-dimethyl-1-(phenylsulphonyl)but-2-ene (16). White crystalline solid, mp 93-94°C. TLC on silica gel (CH_2Cl_2) one spot, Rf.0.46. ^{1}HNMR, MS, IR: section 6.3.9.

11. 2,3-dimethyl-1-(phenylthio)buta-1,3-diene (21). Colourless oil. TLC on silica gel (CH_2Cl_2) one spot. ^{1}HNMR: sections 6.3.10 and 6.3.16. MS: section 6.3.16.

12. 2-acetoxy-2,3-dimethyl-1-(phenylthio)but-3-ene (38). Colourless oil. TLC on silica gel (CH_2Cl_2) one spot Rf.0.4. ^{1}HNMR, MS, IR: section 6.3.12.

13. 2-cyano-2,3-dimethyl-1-(phenylthio)but-3-ene (17). Colourless oil. TLC on silica gel (CH_2Cl_2) one spot, Rf.0.63. ^{1}HNMR, MS, IR: section 6.3.13.

14. methyl 2,3-dimethyl-3-hydroxybutanoate (22). Colourless liquid, bp 66-70°C @ 12-18mmHg. ^{1}HNMR: section 6.4.1.

15. methyl 2,3-dimethylbut-2-enoate (23). Colourless liquid, bp 58°C @ 12mmHg. ^{1}HNMR, MS, IR: section 6.4.2. Similar to those reported in ref.47.

16. 2,3-dimethylbut-2-en-1-ol (24). Colourless liquid. ^{1}HNMR, MS: section 6.4.3, similar to those reported in ref.46.

17. 2,3-dimethylbut-2-en-1-al (20). Colourless oil. ^{1}HNMR: section 6.4.4, similar to that reported in ref.48. DNP: mp 197-198°C (Lit.Ref.48: 198°C, ref.49: 200-201°C). ^{1}HNMR, MS of DNP: section 6.4.4.

18. 2,3-dimethyl-1-(methylthio)but-3-ene-2-ol (27). Colourless oil. TLC on neutral alumina (hexane-CH_2Cl_2 4:1) one spot. ^{1}HNMR: section 6.5.2.

19. 4,4-dimethylcyclohex-2-en-1-one (28). Colourless liquid, solidifies ca.-10°C bp 76-89°C @ 12-22mmHg. ^{1}HNMR, MS, IR: section 6.7.1, similar to those reported in ref.50. DNP: mp 261-262°C, ^{1}HNMR, MS: section 6.7.1.

20. 4,4-dimethyl-1-methylenecyclohexene (29). Colourless liquid, bp 45°C @ 12mmHg. ^{1}HNMR, MS, IR: section 6.7.2.

21. 6,6-dimethyl-1-oxaspiro[2.5]oct-4-ene (30). Colourless liquid, bp ca.70°C 12-20mmHg. ^{1}HNMR, MS, IR: section 6.7.3

further characterised by conversion to 4,4-dimethyl-1-formylcyclohex-1-ene.

22. 4,4-dimethyl-1-formylcyclohex-1-ene (31). Colourless liquid, bp ca.50-60°C @ 11mmHg. ^{1}HNMR, MS, IR: section 6.7.4. DNP mp 231-232°C (lit.236,5°C Ref.51). ^{1}HNMR, MS: section 6.7.4.

23. 1-chloro-4,4-dimethyl-1-(phenylthiomethyl)cyclohex-2-ene (32). Colourless oil. ^{1}HNMR, MS: section 6.7.5.

24. 4,4-dimethyl-1-hydroxy-1-(phenylthiomethyl)cyclohex-2-ene (33) Colourless oil. TLC on silica gel (CH_2Cl_2) one spot Rf.0.63. ^{1}HNMR, MS: section 6.7.6.

25. 4,4-dimethyl-1-hydroxy-1-(methylthiomethyl)cyclohex-2-ene (34). Colourless oil. TLC on silica gel (CH_2Cl_2) one spot. ^{1}HNMR, MS: section 6.7.7.

26. trans-2-chloro-1-(phenylthio)pent-3-ene (35). Light yellow oil. ^{1}HNMR, MS, IR: section 6.8.1, similar to those reported in Ref.45.

27. trans-2-acetoxy-1-(phenylthio)pent-3-ene (36). Light yellow oil. TLC on silica gel (CH_2Cl_2) one spot. ^{1}HNMR, MS, IR: section 6.8.2.

28. trans-2-hydroxy-1-(phenylthio)pent-3-ene (37). Colourless oil. TLC on neutral alumina (CH_2Cl_2-petroleum 1:5) one spot. ^{1}HNMR, MS, IR: section 6.8.3.

6.10 References

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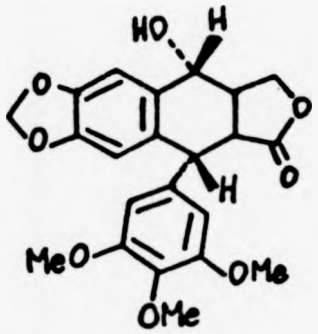
7 Studies of Lignans

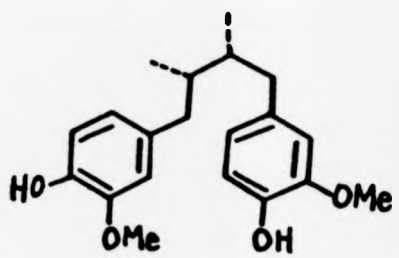
7.1 Lignans From Virola Elongata

Lignans and neolignans are dimeric phenylpropanoids, ubiquitous throughout the plant kingdom[1]. Special interest has been aroused by the biological activity of some members of the group. Podophyllotoxin (1), isolated from Podophyllum emodi[2], possesses marked anti-tumour activity; nor-dihydroguaiaretic acid (2) has been used in cancer therapy[3]; otobain (3) is a fungistatic used in veterinary practice in Colombia[4]; related oxo-otobains have been discovered in the reputedly anti-rheumatic extracts from Virola sebifera[5]. Although many hundreds of lignans are known, their function and biological significance are not well understood. It has been proposed that they are intermediates in the biosynthesis of lignin[16-18], but as yet detailed studies are lacking, and perhaps Goodwin and Mercer[6] are justified in claiming, "Little is known of the biosynthesis of lignans". At the end of this chapter, in fig. 7.7, a proposal for a biosynthetic pathway leading to two of the compounds reported is summarised. This is, however, purely speculative, and further studies are necessary to establish its veracity.

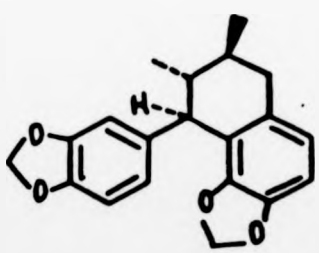
There is some confusion in the nomenclature of lignans. Haworth[7] introduced the term lignan to designate compounds in which the two phenylpropanoid subunits are joined at their β-positions. Neolignans, according to Goodwin and Mercer[8] are compounds in which the phenylpropanoid subunits are joined head-to-tail as in eusiderin (4), rather than tail-to-tail as in lignans (see fig. 7.2).



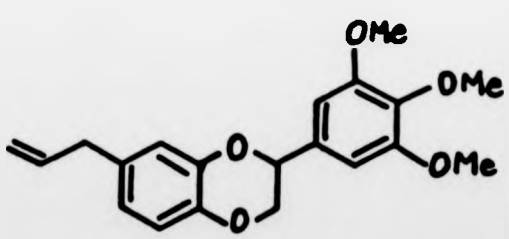
(1) Podophylotoxin



(2) nor-Dihydroguaiaretic acid

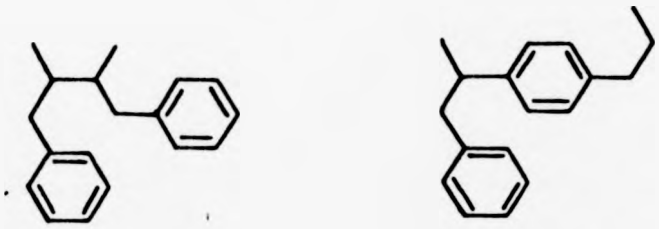


(3) otobain



(4) Eusiderin

Figure 7.1 Lignans and neolignans

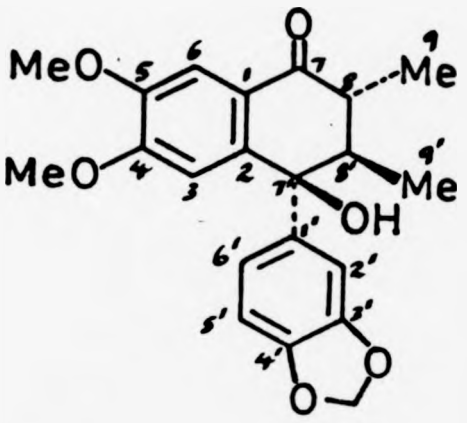


lignans neolignans

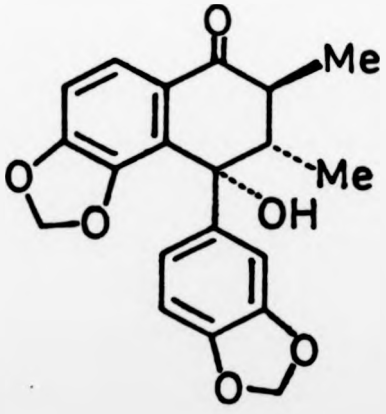
Figure 7.2

Gottlieb[1] employs a systematic nomenclature devised by Freudenberg and Weinges[9], makes a distinction based more on biogenetic rather than structural considerations, and proposes to employ the term lignan for those compounds which arise from the coupling of cinnamic acid or alcohol subunits, while neolignans arise from the coupling of propenyl or allyl-benzene residues. This, however, is obviously unsatisfactory, for compounds with very similar structure could also result from reduction of acid or alcohol derived compounds, as from the biological oxidation of those "neolignans" resulting from coupling of propenyl- or allyl-benzene residues. This confusion can be avoided if we use systematic nomenclature[9], even if we do not, as Gottlieb, proceed to call all phenylpropanoid dimers neolignans, when it would be more appropriate to call them lignans. In this nomenclature the phenylpropane units are identified and numbered 1-9 and 1'-9', and links or bridging oxygens are indicated by pairs of numbers. Thus, podophylotoxin (1) and otobain (3) are 8.8', 7.2', lignans, (2) is an 8.8' lignan, and eusiderin (4) is therefore a 7.0.2', 8.0.3' lignan, or a neolignan.

In the course of phytochemical studies of Colombian Myristicacae[10,21], Martinez and his collaborators isolated three lignans



(6)



(7)

Figure 7.3 Lignans from Virola elongata

Numbering according to Gottlieb[2]

from Virola elongata, and tentatively assigned their structures, from UV, IR and 60MHz ^{1}HNMR measurements*. The samples were brought to the University of Warwick, where 220 MHz ^{1}HNMR and 100 MHz ^{13}CNMR were taken, and to Newcastle, where 300 MHz ^{1}H spectra were obtained. As a result of these measurements their structures could be assigned.

The structures of compounds (6) and (7) were deduced from their spectroscopic data. Both compounds have been reported as constituents of the fruits of V. sebifera[5], and comparison with the published data showed agreement, with one exception. Whereas our melting point for (6) agrees with that published, the value we found for lignan (7) (m.p. 86-87°C) is different from that reported (m.p. 115-117°C)[5]. This is possibly due to different crystalline forms being obtained from different solvents (acetone in our work, methanol in ref. 5). The ^{1}HNMR of compound (6) in $CDCl_3$ (see fig. 5.2) presents absorptions at δ=0.91(d, ^{3}J=6.8Hz), 1.29(d, ^{3}J=6.8Hz), 2.32(dq, ^{3}J=12,6.8Hz) and 2.87(dq, ^{3}J=12,6.8Hz) corresponding to the two methyl groups and the two protons on the ketonic ring. As evidenced by the coupling constants, both methyl groups occupy equatorial positions, and the ring hydrogens present a trans-diaxial interaction. Assuming that the bulky methylenedioxybenzene moiety occupies an equatorial position, the relative stereochemistry is as shown. In the absence of detailed chiroptical information, the absolute stereochemistry is inferred by the agreement of spectra with those published

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* The physical and spectroscopic properties of these compounds are summarised at the end of this chapter.

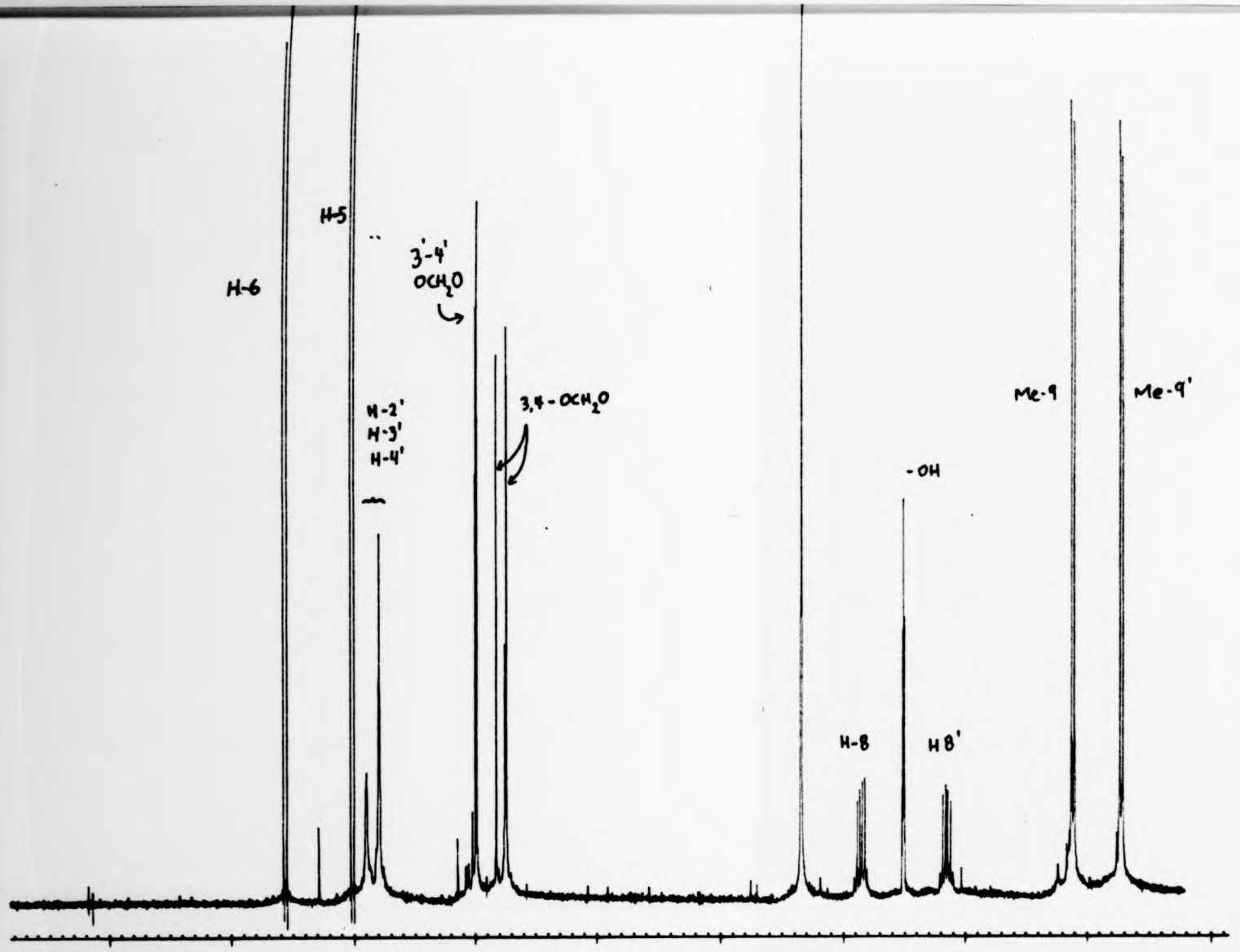

Figure 7.4 The 300MHz ^{1}HNMR spectrum of compound 7

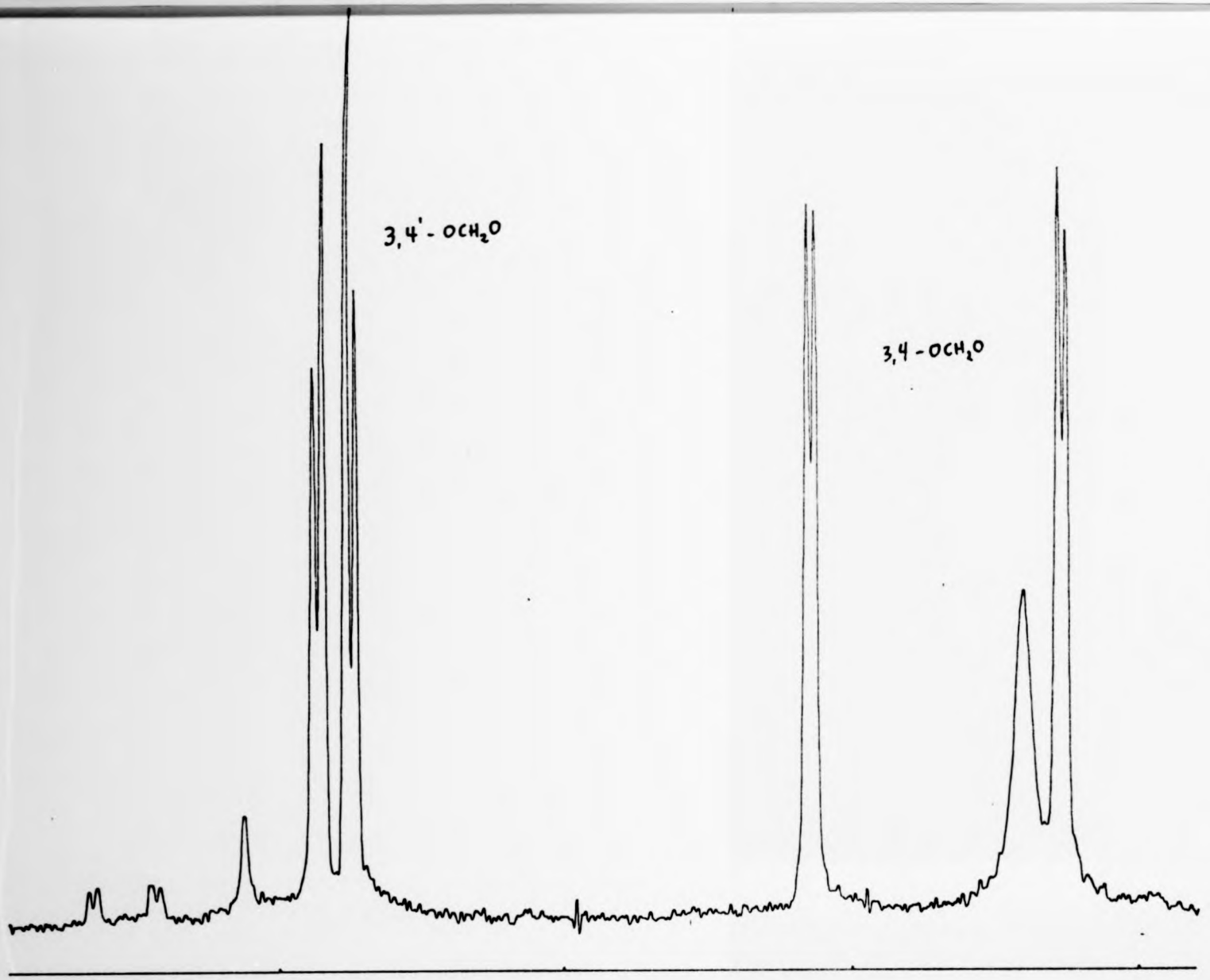

Figure 7.4a Diastereotopic methylenedioxy groups

by Gottlieb and co-workers[5]. Compound (7) shows similar structural features, with an interesting exception. At 200MHz, the spectrum presents two singlets at 5.72 and 5.86, each integrating to one proton. This unusual feature is due to the diastereotopic methylenedioxy group on ring A, in which the ^2J coupling constants are very small. Initially, the two singlets were assumed to arise by the coexistence of two diastereoisomers caused by hindered rotation about the 1'-7' bond. This, however, is not a likely explanation, as careful study of the 300MHz ^{1}HNMR spectrum shows that both sets of methylenedioxy groups have anisochronic protons, giving rise to an AB or and AX system (see fig. 7.3 and 7.4) according to the difference in chemical shift due to the asymmetry of the magnetic environment of the respective protons. The very small ^2J coupling constant seemed puzzling at first, but is well documented for methylenedioxy groups[12,13].

Compound (8) is a new substance, presumably an intermediate in the biosynthetic pathway to (6). Its mass spectrum shows

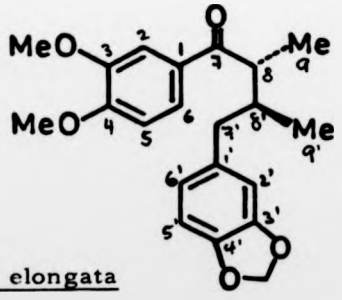

Figure 7.5
New compound from Virola elongata

a peak due to the molecular ion at m/z 356.1629 ($C_{21}H_{24}O_5$ requires 356.1624) and a dominant fragment at m/z 194 which arises from a McLafferty rearrangement (fig.7.6). It UV spectrum in methanol

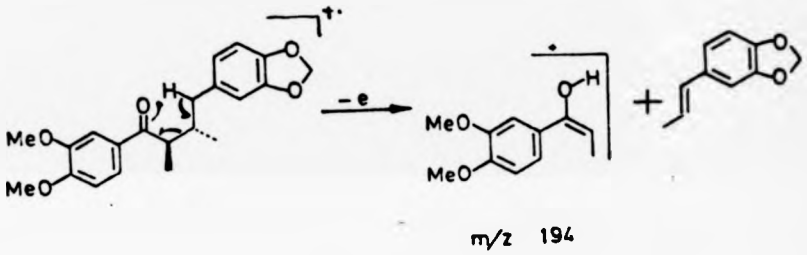

Figure 7.6 McLafferty rearrangement of compounds

shows 2 maxima, at 274nm (ϵ =12500) and 228nm (ϵ =20319) and does not change on addition of sodium hydroxide[20]. This is consistent with two non-interacting aromatic groups, devoid of hydroxy groups on the ring, and a benzylic ketone. The IR spectrum shows a C=0 stretch at 1670cm^{-1}, giving further indication of the benzylic nature of the carbonyl. The 220MHz ^{1}HNMR spectrum shows two methyl doublets, at 0.85 and 1.15ppm, both with ^{3}J=7.0Hz. At 2.25ppm there appears a signal which, when irradiated, causes that at 0.85ppm to collapse to a singlet. This signal at 2.25ppm is a double double double quartet: a quartet by coupling to the CH_3 at 0.85ppm, doubled twice by ^{3}J couplings to both protons at C-7', and doubled for a third time by a ^{3}J coupling to the proton at C-8. The four couplings are 7.8, 7, 7 and 7Hz, respectively. The proton at C-7, however, resonates at 3.38ppm as a double quartet (J=7 and 7Hz). The diastereotopic methylene groups resonate at 2.43 and 2.58, generating double doublets with ^{2}J=14.4Hz, and ^{3}J=7.8Hz. The rest of the spectrum is straightforward, with the two methoxy groups at C-3 and C-4 resonating at 3.90 and 3.95ppm, and the methylenedioxy group at C-3' and C-4' giving a singlet at 5.94ppm. The aromatic protons at C-2', C-5' and C-6' resonate as a multiplet from 6.6-6.9ppm, H-5 gives rise to a doublet (^{3}J=9.5Hz) at 6.84ppm, and H-6 a double doublet at 7.37ppm (^{3}J=9.5Hz, ^{4}J=1.5Hz) and H-2 a broad singlet at 7.45ppm.

The ^{13}CNMR spectra were assigned (see Section 7.2) by analogy to those of known compounds[13-15], and they confirm our structural assignment.

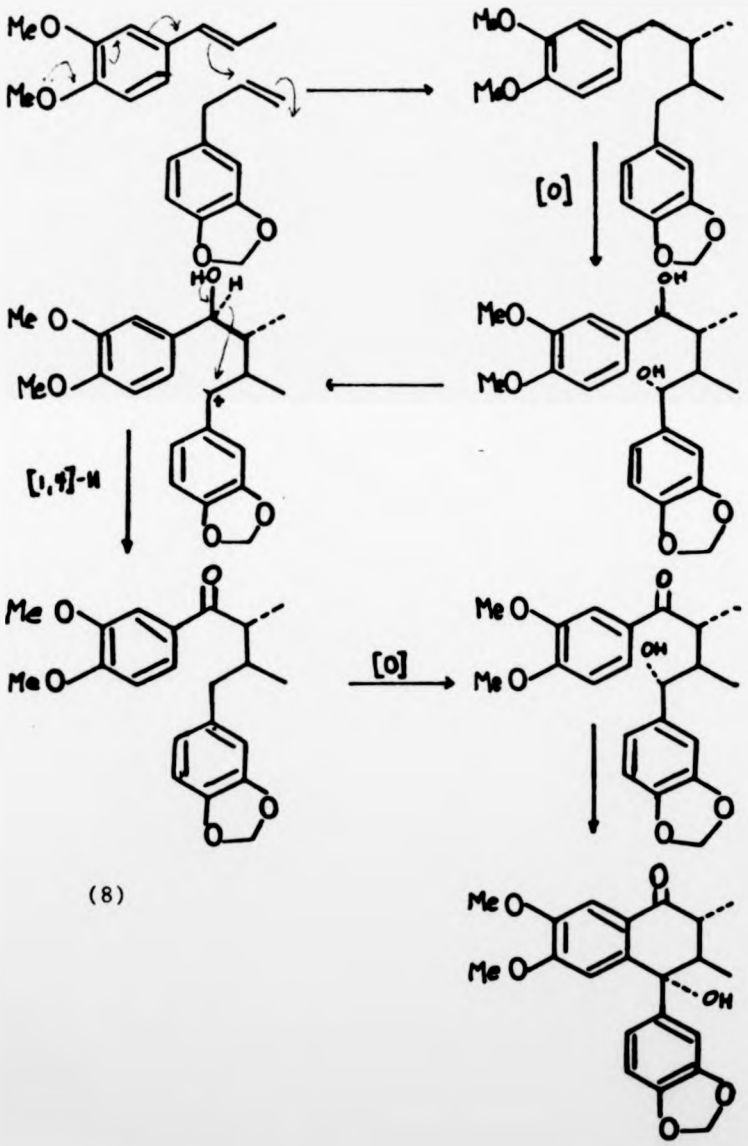

Figure 7.7 Proposed biosynthetic route to compounds (8) and (6)

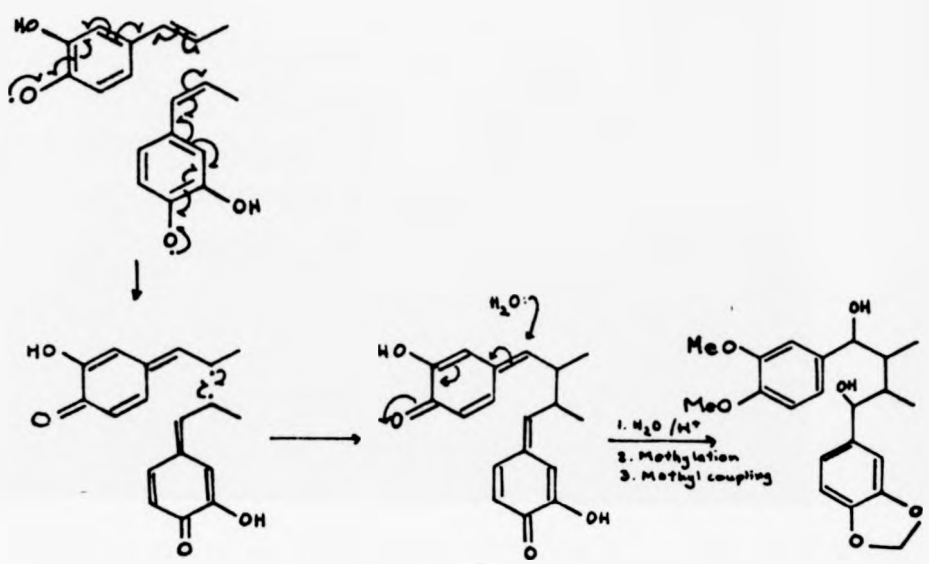

Figure 7.7a

The prevalent idea concerning the biosynthesis of lignans is an oxidative coupling of phenols. This appears in most textbooks, although there is very little evidence to support this mechanism in vivo. Further studies are necessary to determine which is the actual pathway of the biosynthesis of lignans.

7.2 Experimental

The plant samples of Virola elongata (Benth.) Warburg[19] were collected in the Vaupés region of Colombia, and compounds (6) - (8) were obtained by chromatography of the benzene extracts of the bark by J.C.Martinez, L.E.Cuca and A.Santana.

(2R, 3R, 4S)-4-Hydroxy-2,3-dimethyl-6,7-dimethoxy-4-piperonyl-1tetralone (6). White crystals (75mg) m.p. 177-179°C (acetone) (lit. m.p. 177-180° [5]). R_f 0.2 (silica gel, benzene-ethyl acetate 4:1). λ_{max}^{MeOH} nm (ϵ): 312 (6650), 278 (12400), 233 (21000). $\lambda_{max}^{MeOH+NaOH}$ nm (ϵ): 312 (6650), 278 (12400), 233 (21000). ν_{film}^{max} cm^{-1}: 3600, 3500, 3000, 1680, 1605, 1510, 1490, 1450, 1410, 1370, 1275, 1240, 1160, 1135, 1045, 1020, 990, 940, 890, 820. MS similar to that reported [5].

^{1}HNMR(220MHz,$CDCl_3$,δ) 7.52(s,H-6), 6.86(m,H-2',H-5',H-6'), 6.3(s,H-3) 6.0(s,3',4'-CH_2O_2), 3.93(s,4-OMe), 3.68(s,5-OMe), 2.87 (dq,J=12Hz,6.8,H-8), 2.32(dq,J=12Hz,6.8,H-8') 2.12(s,7'-OH), 1.29 (d,J=6.8Hz,9-Me), 0.91(d,J=6.8Hz,,9'-Me), ^{13}CNMR(100MHz,$CDCl_3$, δ) 125.2(1-C) 140.0(2-C), 108.3(3-C), 152.9(4-C), 149.2(5-C), 110.7(6-C), 198.6(7-C), 46.9(8-C), 12.9(9-C), 56.0(5-OMe), 55.9 (4-OMe), 141.8(1'-C), 107.4(2'-C), 147.4(3'-C), 146.4(4'-C), 107.5 (5'-C), 119.9(6'-C), 76.8(7'-C), 43.3(8'-C), 12.4(9'-C), 101.0(3', 4'-O_2CH_2). (2R,3R,4S)-4-Hydroxy-2,3-dimethyl-5,6-methylenedioxy-4-piperonyl-1-tetralone (7). White crystals (208mg). M.p. 86-87° (acetone) (lit. m.p. 115-117° (MeOH) [5]). R_f 0.32 [system as for (6)]. λ_{max}^{MeOH}nm (ϵ): 305 (6600), 280 (9375), 232 (22222). $\lambda_{max}^{MeOH+NaOH}$ nm (ϵ): 305 (6600), 280 (9375), 232 (22222). ν_{max}^{film} cm^{-1}: 3470, 2980, 2890, 1680, 1620, 1590, 1500, 1490, 1450,

1300, 1250, 1040, 1000, 940, 910, 885, 810, 750. MS m/z (%): 354(M^+,36.7), 355$(M+1)^+$ (7.98), 356 $(M+2)^+$ (1.34), 298 (100), 269 (7.0), 240 (10), 212 (4.0), 149 (28), 120 (8.0), 91 (5.0). ^{1}HNMR (220MHz,$CDCl_3$,) 7.72 (d,J=8.0Hz,H-6), 6.88 (d,J=8.0Hz, H-5), 6.65-6.75 (m,H-2',H-3',H-4'), 5.97 (s,3',4'-O_2CH_2), 5.85 (s,1 x 3,4-O_2CH_2), 5.72 (s,1 x 3,4-O_2CH_2), 2.83 (dq,J=12Hz,6.8, H-8), 2.18 (dq,J=12Hz,6.8,H-8'), 2.43 (s,7'-OH), 1.20 (d,J=6.8Hz, Me-9), 0.95 (d,J=6.8Hz,Me-9'), ^{1}HNMR (300MHz, d-6DMSO, 32K points, GAUSSIAN line narrowing, k_T=0.35, LB=-1.0Hz, δ) 7.55 (d,J=8.2Hz,H-6), 7.00 (d,J=8.2Hz,H-5), 6.7-7.0 (br m,H-2',H-3', H-4'), 5.99 (d,J=0.99Hz,1 x 3',4'-O_2CH_2), 5.98 (d,J=1.00Hz,1 x 3', 4'-O_2CH_2), 5.81 (d,J=0.79Hz,1 x 3,4-O_2CH_2), 5.73 (d,J=0.78Hz, 1 x 3,4-O_2CH_2), 2.84 (dq,J=12.4,6.5Hz,H-8) 2.14 (dq,12.3,6.7Hz, H-8'), 1.11 (d,J=6.7Hz,Me-9), 0.72 (d,J=6.7Hz,Me-9'). ^{13}CNMR (100MHz,$CDCl_3$, δ) 126.6 (C-1), 128.5 (C-2), 144.6 (C-3), 152.4 (C-4), 108.8 (C-5), 118.9 (C-6), 198.4 (C-7), 46.8 (C-8), 12.1 (C-9), 101.9 (3,4-O_2CH_2), 140.4 (C-1'), 106.6 (C-2'), 147.2 (C-3'), 146.2 (C-4'), 107.4 (C-5'), 122.8 (C-6'), 74.7 (C-7'), 43.3 (C-8'), 12.0 (C-9'), 100.8 (3',4'-O_2CH_2). 1-(3,4-Dimethoxyphenyl)-2,3-dimethyl-4-piperonylbutan-1-one (8). Pale yellow oil (238mg). R_f 0.54 (silica gel, petrol-ethyl acetate 85:15) (M^+ found: 356.1629: $C_{21}H_{24}O_5$ requires 356.1624) λ_{max}^{MeOH} nm (ϵ): 274 (12500), 228 (20319); $\lambda_{max}^{MeOH+NaOH}$ nm (ϵ): 274 (12500), 228 (20319). $^{max}_{film}$ cm^{-1}: 2950, 1670, 1600, 1510, 1490, 1450, 1420, 1360, 1260, 1210, 1170, 1130, 1030, 930, 880, 860, 810, 790, 755. MS m/z (%): 356 (7), 194 (100), 165 (27), 135 (16.9), 77 (10), 28 (11). ^{1}HNMR (60MHz, $CDCl_3$, δ), 7.32 (m,H-6,H-2), 6.85 (br s,H-5), 6.65 (br s,H-2',H-5', H-6'), 5.88 (s,O_2CH_2), 3.90 (s,MeO-3), 3.85 (s,MeO-4), 2.0-3.7 (m,2 x H-7',H-8,H-8'), 1.15 (d,J=6.5Hz,Me-9) 0.85 (d,J=6.5Hz,

Me-9'). ^{1}HNMR (220MHz,$CDCl_3$, δ) 7.45 (s,broad,H-2), 7.37 (dd,J=9.5 and 1.5Hz,H-6) 6.84 (d,J=9.5Hz,H-5), 6.70 (m,H-2',H-5', H-6'), 5.94 (s,O_2CH_2), 3.95 (s,MeO-3), 3.90 (s,MeO-4), 3.38 (dq,J=7.0,H-8), 2.58 (dd,J=14.4 and 7.8Hz,H-7'), 2.43 (dd,J=14.4 and 7.8,H-7'), 2.25 (dddq,J=7.8,7,7 and 7,H-8'), 1.15 (d,J=7.0, Me-9), 0.85 (d,J=7.0,Me-9'). ^{13}CNMR (100MHz,$CDCl_3$, δ), 129.7 (C-1), 110.5 (C-2), 148.9 (C-3), 152.9 (C-5), 122.4 (C-6), 202.4 (C-7), 42.8 (C-8), 14.8 (C-9), 55.7 (3-OMe), 55.8 (4-OMe), 134.5 (C-1'), 108.0 (C-2'), 147.4 (C-3'), 145.6 (C-4'), 109.4 (C-5'), 121.9 (C-6'), 37.4 (C-7'), 41.2 (C-8'), 11.2 (C-9'), 100.5 (3',4'-O_2CH_2).

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Appendix 1: Computer-Assisted Organic Chemistry

A.1.1 The Context

In the period during which the research described in this thesis took place, considerable use was made of several computer-based facilities. Because most of these facilities are housed in remote host computers, access to them had to be obtained through the S.E.R.C.'s Joint Academic Network (JANET) or via ordinary telephone lines.

The systems employed were of two distinct types: purely mechanical calculations or database searching procedures and knowledge-based expert systems[1,8]. The results obtained from calculations and database searching were displayed through the graphics interface programs VIEW[2] and MODEL[3].

The databases used were the Fine Chemicals Directory[2](FCD), the Crystal Structure Search and Retrieval[2](CSSR) and the C-13 NMR spectra database (CNMR). Molecular co-ordinates obtained from the crystal structure Data File with CSSR were displayed with VIEW or MODEL.

ORAC[4,8] is an organic reaction retrieval system, developed by Dr A.P.Johnson at the University of Leeds. This system allows search of a chemical reaction database with great versatility, as not only keyword searches are possible, but also structure and sub-structure searches can be activated through simple interactive graphics procedures.

LHASA[8], a retrosynthetic analysis expert system, has also been used.

In this thesis we report the results of molecular mechanics calculations on β-phellandrene and β-turmerone. The programs used for this purpose were E.K.Davies' molecular mechanics program, which forms part of the CHEMGRAF suite, and Allinger's MM2(82) program[5]. The difference between these two programs lies in the extent of the parametrisation. Davies' version is not suitable for highly strained structures, and sp^2-sp^2 bonds are treated as aromatic, unless the parameters are modified by the user. The results are applicable to geometrical and internal energy properties of a wide variety of molecules. Allinger's version is more fully parameterised[7], and calculations with it demand more computer time than with Davies'. Both methods employ a minimisation algorithm[7] to obtain values of energy minima. In principle, the energy structure can be minimised by bond shifts and rotations to give the lowest minimum of the system in one calculation. In practice, however, the minimisation procedure often results in structures which represent local minima. This feature is useful for a detailed study of the conformational space available to a particular molecule, but when minimum energy conformations are searched for, local minima may be obtained instead. This demands considerable caution in the interpretation of results from a single MM2 minimisation of a complex molecule. To avoid confusion, therefore, it is necessary to repeat the calculation with alternative geometries and these new geometries may be easily generated from within MODEL. In the next section, we describe the exact procedure employed for obtaining the minimum-energy conformations for the turmerones.

In general, the initial atomic co-ordinates are produced by the LHASA graphics interface. This generates a file whose structure is incompatible with either MM2 or MODEL. File-conversion programs exist as facilities on the Wolfson Vax 11-750 at Leeds[4].

A.1.2 Instructions for using MM2[9,10]

Detailed instructions for the use of the program may be found in ref.10, as well as in the appropriate documentation.

A.1.3 Results of the Calculations

Here follow the results of the molecular mechanics calculations on β-phellandrene and β-turmerone. Bond lengths, bond angles and dihedral angles are listed consecutively. The numbering is arbitrary, and refers to the atom numbers in the accompanying diagrams.

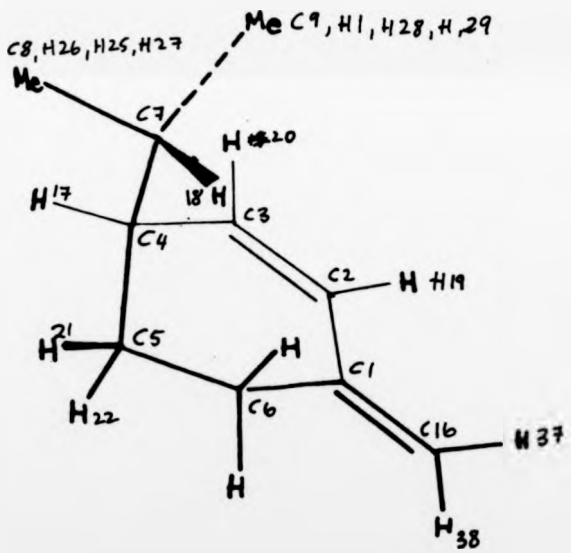

Figure A1.3.1 Pseudo-axial conformation of β-phellandrene with 147° H17-C4-C7-H18, minimum at 0.172505E + 03kcal

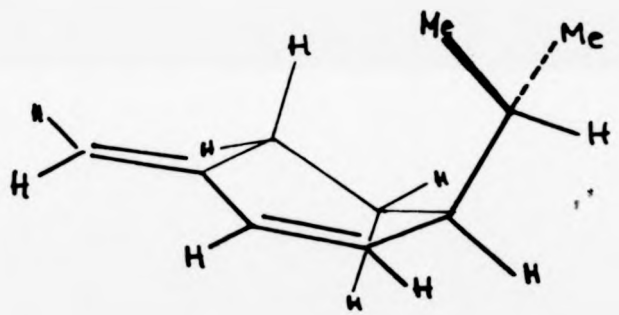

Figure A1.3.2 Pseudoaxial conformation of β-phellandrene with H17-C4-C7-H18 -34° MME=0.12591E + 03kcal

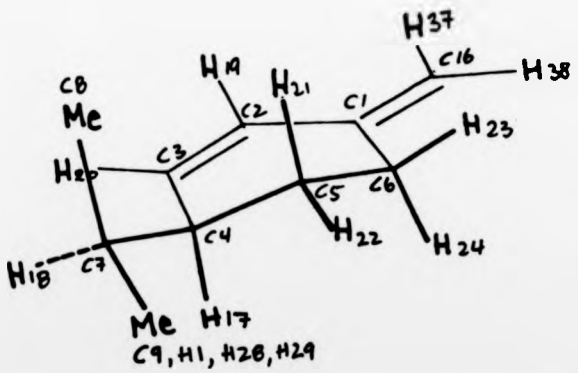

Figure A1.3.3 Pseudoequatorial conformation of β-phellandrene for H17-C4-C7-H18 -81°, MME=0.132500E + 03kcal

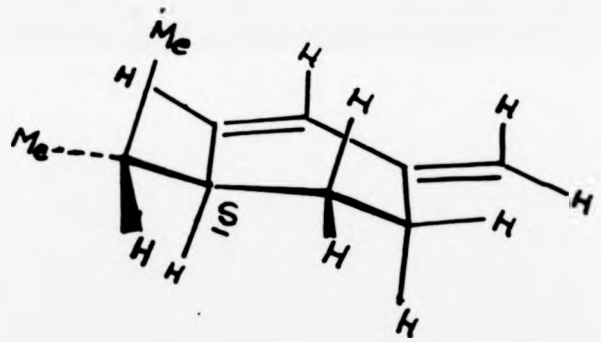

Figure A1.3.4 Pseudoequatorial conformation of β-phellandrene

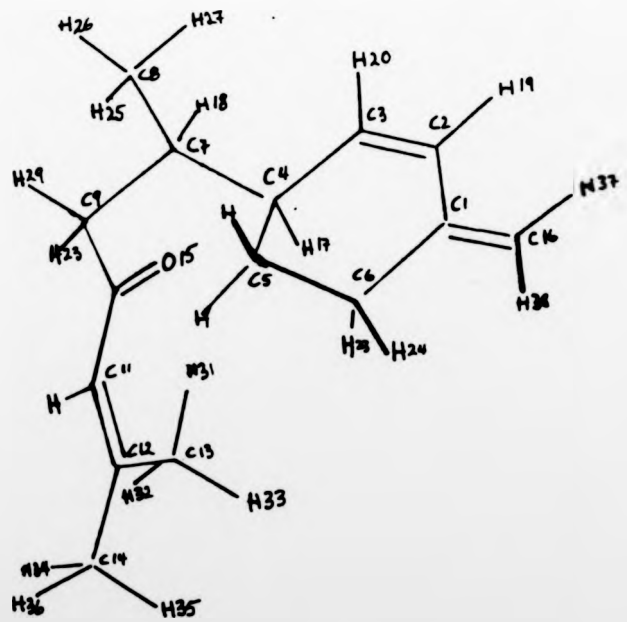

Figure A1.3.5 Allinger MM2 minimised (R),(S)- β-turmerone

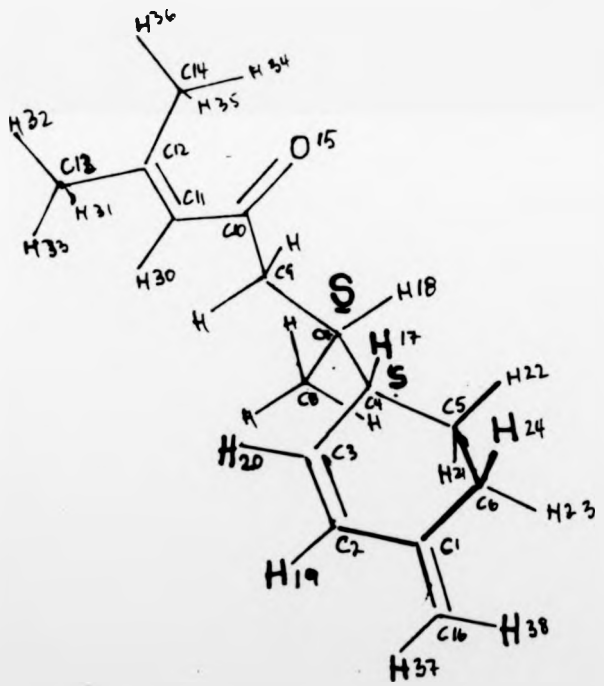

Figure A1.3.6 Allinger MM2 minimised (S),(S)-β-turmerone

Molecular mechanics energy = 3.5285235E+02 kcal/m

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Turmerones: Isolation from Turmeric and their Structure Determination

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The presence of two turmerones in turmeric is demonstrated and their structures are defined as 2-methyl-6-(4-methylcyclohexa-2,4-dien-1-yl)hept-2-en-4-one (**5**, 'α-turmerone') and 2-methyl-6-(4-methylenecyclohex-2-en-1-yl)hept-2-en-4-one (**2**, 'β-turmerone').

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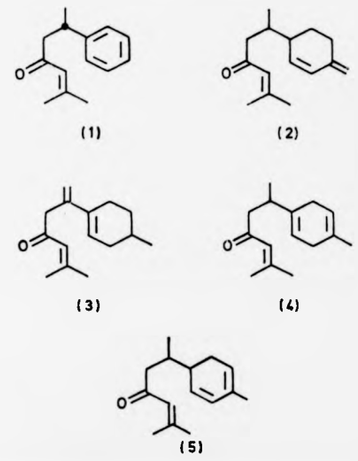
Turmeric, from the Rhizomes of *Curcuma longa* has been known for its colouring, flavouring, and digestive properties since at least the second millenium B.C.[1] It is a constituent of curry powders and contributes to their characteristic colour and odour. Nearly fifty years ago,[2] the major constituents of the essential oil of turmeric were recognised to be ketonic sesquiterpenes $C_{15}H_{22}O$ and $C_{15}H_{20}O$. The structure of the former was shown[3] to be (**1**) and it was called ar-turmerone. The latter, known as turmerone, was considered to have the enone and carbon skeleton of (**1**) but the aromatic ring was partially reduced. However, it was not possible to isolate it in pure form, to locate its double bonds, or even to be sure that it was a single isomer. Later, it was reported that turmerone could be isolated *via* an inclusion compound with thiourea, and from the evidence of u.v. and i.r. spectra the structure was assigned as either (**2**) or (**3**).[4] Structure (**4**) has also been proposed[5] and is the basis for the current Chemical Abstracts name (Reg. Number 56485-42-8).

We report here the isolation and spectroscopic characterisation of two isomeric turmerones to which we assign the structures 2-methyl-6-(4-methylcyclohexa-2,4-dien-1-yl)hept-2-en-4-one (**5**) and 2-methyl-6-(4-methylenecyclohex-2-en-1-yl)hept-2-en-4-one (**2**). We give these compounds the trivial names α- and β-turmerone, respectively, by analogy with their lower prenylogues, the phellandrenes.

Flash chromatography[6] [silica gel 60, 1% triethylamine† and 5% ether in light petroleum (b.p. 40—60 °C)] of turmeric oil gave a fraction of turmerone free from ar-turmerone, which was further fractionated by h.p.l.c. (Hichrom S5W-500SP, 1% triethylamine† in hexanes). The low value for the relative retention times of the major turmerones ($\alpha = 1.11$) and the presence of minor components (see below) made separation of the turmerones very difficult and recycling (8—10 times) was necessary to obtain pure α- and β-turmerone, albeit in only milligram amounts.

The faster eluting component was shown by high resolution mass spectrometry to have the formula $C_{15}H_{22}O$.. Bands at 1681 and 1627 cm^{-1} in the i.r. spectrum and a coupled spin system in the ^1H n.m.r. spectrum [δ($CDCl_3$) 6.05 (1 H, septet, *J* 1.3 Hz), 2.14 (3 H, d, *J* 1.3 Hz), and 1.89 (3 H, d, *J* 1.3 Hz)]

† In the absence of triethylamine, silica gel caused isomerisation and degradation of the turmerones.



show the presence of the Me_2C=CHCOX fragment where X is a saturated carbon atom. The other signals at low field [δ 5.79 (1 H, dt, *J* 10, 2 Hz), 5.63 (1 H, dd, *J* 10, 3 Hz), and 5.42 (1 H, broad s, Σ*J* 16 Hz)] and the 3 H multiplet at δ 1.72 are very similar in their chemical shift and multiplicity to four resonances in the spectrum of α-phellandrene,[7] and show that α-turmerone has a 4-methylcyclohexa-2,4-dien-1-yl fragment. Interpretation of the remaining high field regions of the ^1H n.m.r. spectrum secures structure (**5**). The u.v. spectrum of (**5**) before and after the addition of sodium borohydride and the difference spectrum gave λ_{max} (enone) 238 nm and λ_{max} (diene) 261 nm, which compare well with data for mesityl oxide (λ_{max} 237 nm) and α-phellandrene (λ_{max} 263 nm).

For the slower eluting component, mass spectrometry confirmed the molecular formula $C_{15}H_{22}O$, and the fragment Me_2C=CHCOX was indicated by i.r. bands at 1681 and 1626 cm^{-1} and the coupled ^1H spin system [δ(C_6D_6) 5.83 (1 H, septet, *J* 1.2 Hz), 2.16 (3 H, d, *J* 1.2 Hz), and 1.51 (3 H, d, *J* 1.2 Hz)]. The remaining four low field signals [δ 6.24 (1 H, dd, *J* 10, 2 Hz), 5.61 (1 H, d, *J* 10 Hz), 4.87 (1 H, s), and 4.82 (1 H, s)] define the nature of the 6-membered ring as in (**2**). A similar u.v. study to that described for (**5**) gave λ_{max} (enone) 237 nm and λ_{max} (diene) 232 nm [*cf.* mesityl oxide (λ_{max} 237) and β-phellandrene (λ_{max} 232 nm)] and an i.r. band at 881 cm^{-1} confirmed the exo-methylene group of (**2**). The question of the configurations at the chiral centres in (**2**) and (**5**) is currently under study.

Careful comparison of the low field regions of the ^1H n.m.r. spectra of crude turmeric oil, the turmerone fraction from flash chromatography, and the isolated ar-, α-, and β-turmerones showed that these three compounds are not artefacts, but are, indeed, the major components of the crude oil, and that other minor components are present in the turmerone fraction from flash chromatography. G.l.c.–mass spectroscopic analysis of that fraction showed a single peak in the mass chromatogram for *m/z* 216 (ar-turmerone), whereas for *m/z* 218 there were two major, one minor, and other trace peaks.

We thank Schwartz Spices Ltd. for a generous gift of turmeric (Allepey fingers), the British Council for an award to E.P., the S.E.R.C. for access to the regional n.m.r. service (Warwick), and Drs. E. H. Curzon and O. W. Howarth for assistance with the recording of 400 MHz ^1H n.m.r. spectra.

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